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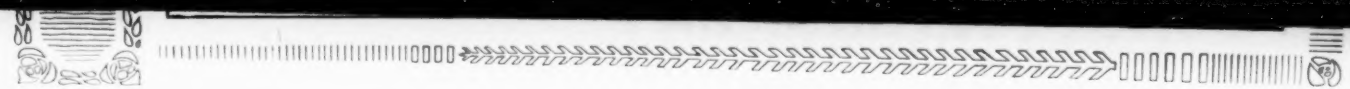

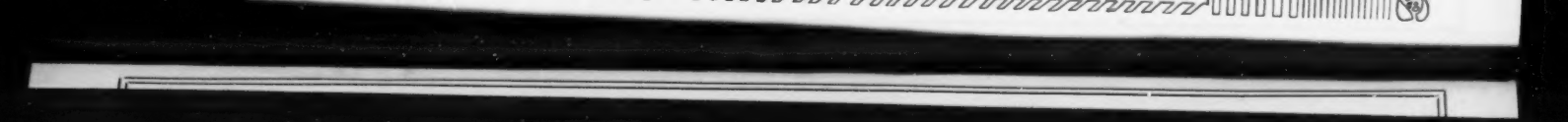

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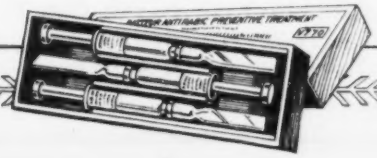

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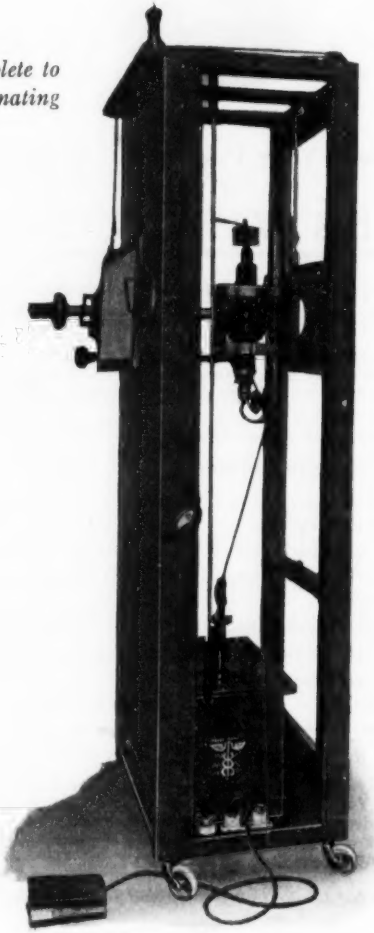

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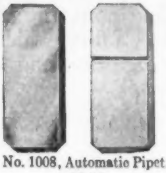

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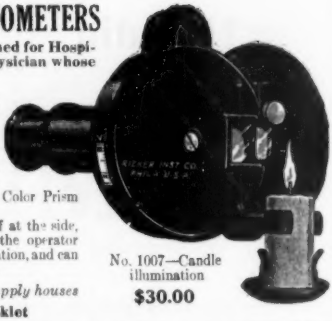

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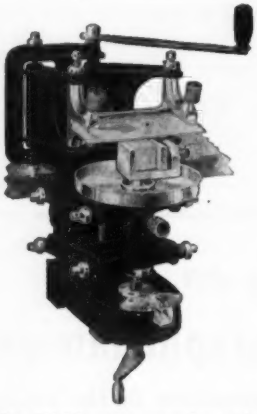

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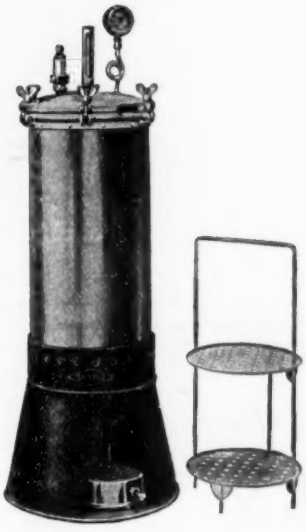

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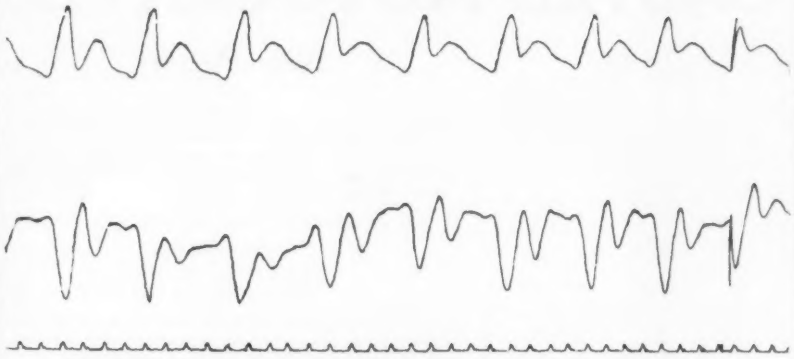

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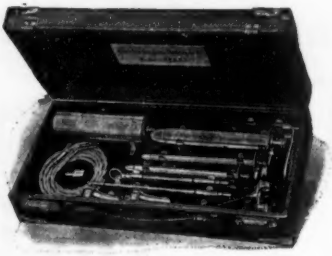

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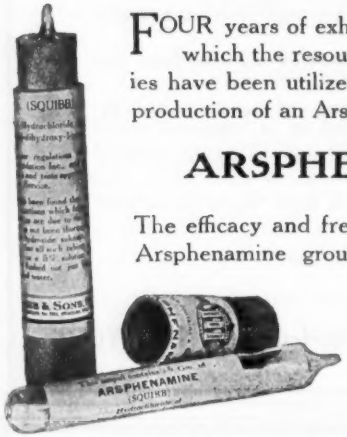

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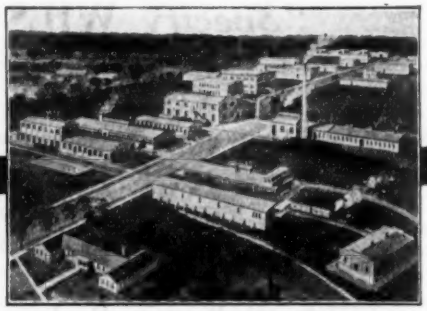

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APRIL, 1921

ORIGINAL ARTICLES.

PELLAGRA.

By Ward J. MacNeal, Ph.D., M.D.,

PROFESSOR OF PATHOLOGY AND BACTERIOLOGY AND DIRECTOR OF THE LABORATORIES, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL.

Definition. Pellagra is a specific disease of man characterized by clinical manifestations on the part of the digestive tract, the nervous system and the skin. The digestive tract presents various grades of inflammation. The nervous system manifests varying grades of toxic reaction, ranging from peripheral neuritis to toxic psychosis, or the lethal central neuritis. The cutaneous eruption is the most characteristic feature of pellagra. It is a symmetrical erythema involving especially the backs of the hands, and it has the same importance in the diagnosis of pellagra as has the eruption of measles or of smallpox in the diagnosis of those diseases.

Etiology. *Specific Causation.* The specific cause of pellagra is unknown. There are numerous theories championed by one or more students of the disease, some of them definite, others quite nebulous. Roussel, in 1866, presented the zeistic theory in such definite form and supported it by such clearly marshalled facts that from his day until 1905 this conception of pellagra remained almost unchallenged. According to Roussel, pellagra is due to two factors or groups of factors, of which one is external and the other resides within the human body itself. The extrinsic factor is altered maize, which is the special and specific cause of pellagra, giving to the disease its character as a pathologic entity and without which the other etiologic factors are powerless to produce this malady. However, in order to be effective, the altered maize is not alone sufficient,

since observation proves that its abundant use often fails to produce pellagra; it requires in addition to encounter within the body of the victim certain conditions of vitality, just as parasites need to encounter appropriate susceptible hosts and as seeds require suitable soil for their development. All causes of enfeeblement, particularly the phases of sexual activity in the female and above all the factor of heredity, create this necessary vital condition of susceptibility. Such, says Roussel, is the dual basis indispensible as a solid foundation for the etiologic theory of pellagra. Much in this view of Roussel still merits admiration and respectful consideration. In 1905 Sambon launched a most effective attack against the maize theory, and it is now almost universally recognized that pellagra occurs in those who do not eat maize, the possibility of which was absolutely denied by Roussel in his time. Sambon, unfortunately, coupled with his refutation of the maize theory the thesis that pellagra is an insect-borne infectious disease, transmitted by a fly of the genus Simulium, a theory which has not been able to survive in the subsequent study of pellagra.

In 1911 the Illinois State Pellagra Commission, after extensive studies of outbreaks of pellagra in institutions for the insane over a period of two years, drew the following conclusions:

1. According to the weight of evidence pellagra is a disease due to infection with a living microörganism of unknown nature.
2. A possible location for this infection is in the intestinal tract.
3. Deficient animal protein in the diet may constitute a predisposing factor in the contraction of the disease.

This commission recommended an increase in the animal protein of the dietaries of the state hospitals and advised compulsory notification of all cases of pellagra. The Robert M. Thompson Pellagra Commission, after extensive study of pellagra in the general civilian population of the Southern United States and in the West Indies, in the course of which particular attention was given to the maize theory and to Sambon's theory of insect transmission, has come to conclusions supporting the Illinois Commission. Jobling and Peterson and their co-workers, as a result of their extensive epidemiologic studies in Nashville and vicinity, also incline to the same view.

Sandwith, in 1912, raised the question whether pellagra might not be a disease essentially due to a deficiency of nutrition, and he pointed out certain analogies between pellagra and beriberi. This theory has been enthusiastically supported by Funk and by Goldberger and their followers. Particularly striking evidence in favor of this theory is found in the elimination of pellagra from eleemosynary institutions by radical improvement of the dietary. That such results admit of another interpretation is evident, as was pointed out by the Illinois Commission in 1911. In November, 1916, Goldberger and Wheeler announced the experimental production,

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by means of a deficient unbalanced diet, of a "typical" eruption justifying a diagnosis of pellagra in six of eleven human subjects experimented upon. Because of the official position of these authors this definite and positive announcement, although a mere preliminary communication unaccompanied by detailed facts and illustrations, received wide recognition as a real and valid discovery. The full report, which has now appeared after a delay of more than three years, reveals that what the authors at first designated as a "typical" eruption was actually a dermatitis on the scrotum and apparently on the opposed surfaces of the thighs also in some of the individuals. Apparently the authors no longer wish to maintain that this is a "typical" eruption justifying the diagnosis of pellagra, for in the full report they avoid this expression, and furthermore even express a doubt as to whether their experimental diet was of the specific quality necessary to cause the usual eruption of pellagra. Sullivan made a biologic study of the diet employed by Goldberger and Wheeler, and with it he induced polyneuritis and paralysis in experimental animals, which condition he was able to prevent and even to relieve after its development by the administration of extracts of rice polishings. McCollum, who with his collaborators has carried out an extensive series of studies upon diets of this type, has finally expressed his conviction that pellagra is an infectious disease.

Perhaps the most serious difficulty for the deficiency theory has arisen during the period of the recent war. Dietary deficiency became the rule in central Europe and the resulting increase in debility and in death-rate have been conspicuously reported. Among the diseases increased in this part of Europe during the period of deficient diet, pellagra is conspicuously absent. Actually there was observed an extensive outbreak of pellagra in a British camp for Turkish prisoners of war located in Egypt. Many of these prisoners had evidently been pellagrins before capture, but the disease also spread to new victims in the prison camp. This outbreak of pellagra was investigated by a British Committee of Inquiry, and they ascribed it to the relatively deficient diet of the Turkish prisoners, contrasting, in their report, their condition with that of the German prisoners in an adjacent camp, men who had subsisted on a most excellent diet before capture and who were receiving as prisoners a diet above reproach. Enright has since reported an extensive outbreak of pellagra in this very camp of German prisoners, the outbreak having begun at almost the exact time that the above-mentioned Committee of Inquiry had completed its investigations, namely, December, 1918, and January, 1919. Enright concludes, "Although I have been unable to advance any satisfactory cause for this mysterious outbreak of pellagra, I do submit that I have established a clear case against a 'food deficiency' as being the only factor involved."

In my own opinion the etiology of pellagra depends upon two factors analogous to those recognized by Roussel: (1) The specific causative factor which is a living organism, an infectious agent derived directly or indirectly from a previous case of the disease, and (2) a factor or group of factors, quite non-specific, which serve to reduce the resistance of the victim. In this latter group are recognized malnutrition, either from inadequate food or inability to utilize food in an adequate manner, cachexia of disease, overwork, depressing influence of hot weather, strain of reproduction in women, involution of old age, alcoholism and many other such influences. The specific causative factor, which I believe to be a living organism, remains unrecognized. Most probably it resides in the gastro-intestinal tract, and the absorption of its products from the digestive tract gives rise to the distant manifestations of pellagra. In regard to the factors influencing the possible transmission of the hypothetical parasite, as well as those which may influence the resistance of the human individual, a great many facts have become established by epidemiologic studies in pellagrous districts, some of which are next to be considered.

Geographical Location. Isolated cases of pellagra are occasionally observed in various parts of the world. In view of the chronic and recurrent nature of the disease and the extent of modern travel, such observations are to be expected. In general, however, the relationship between place and origin of pellagra is one of the most striking features of the disease. Pellagra is contracted where there is a preëxisting case of the disease. Its apparent sporadic origin is so rare as to warrant a grave doubt as to the accuracy of diagnosis or the adequate search for preëxisting cases in such instances. Of the thousands of children suffering from malnutrition and lack of food seen every year in the hospitals and clinics of large cities outside pellagra districts, none suffer from pellagra. In pellagrous districts, on the other hand, a very considerable proportion of persons, and especially the children, suffering from lack of food, diseases associated with malnutrition or other depressing conditions, contract pellagra.

Pellagra is prevalent in certain parts of Turkey, Egypt, Roumania, Austrian Tyrol, Northern Italy, West Indies, Yucatan and the Southern United States. Outbreaks have been reported in South Africa and in the Malay States. Outbreaks of considerable importance and sometimes persisting for several years have been observed in the Northern United States, especially in institutions for the insane. In the geographic areas where the disease prevails its distribution is extremely uneven.

Even in the small communities where pellagra is most prevalent the degree of proximity to a pellagrin shows a significant relationship to the danger of contracting the disease. Thus the Thompson-McFadden Commission, in 1913, observed a pellagra incidence of

6.59 per cent. among persons living in the same house with a pellagrin, 1.72 per cent. among persons living next door to such a house and 0.52 per cent. for those living farther away than next door but in the same village communities. This house relationship of pellagra has been confirmed by the subsequent third report of the same commission and also by the independent work of Jobling and Peterson.

Race, Age and Sex. The relationship of race to pellagra is apparently in part directly dependent upon racial variation in resistance to the disease, but in part indirect because one race may be relatively segregated, may be less prosperous or may live upon poorer food. In Spartanburg County, South Carolina, up to October 15, 1914, the negro population of 28,507 had shown 153 recorded pellagrins, an incidence rate of 54 per 10,000, whereas the white population of 62,119 had shown 1027 recorded pellagrins, an incidence rate of 165 per 10,000. This lower incidence in negroes occurred in conjunction with greater poverty of this race and a diet poorer in quality, quantity and variety. The negro population was for the most part relatively segregated from the white race, and thus from the white pellagrins and the incidence of pellagra in the negroes was lowest in those sex and age groups most completely segregated in this way. Although much less frequently attacked by pellagra, the negroes when attacked suffered most severely. Of the 153 cases in negroes, 64, or 41.8 per cent., terminated in death in the first year of the disease, whereas in the white race the analogous death-rate was only 12 per cent. The higher death-rate may express a lower racial resistence to pellagra, but, in part at least, it would seem to be correlated with the greater poverty and the poorer diet of the negro race. No less than 113 of the 153 negro cases occurred in females over sixteen years of age, namely, that portion of the negro race which is least effectively segregated from the white race.

The age at onset of pellagra in each race and sex in the Spartanburg statistics is indicated in Figs. 1, 2 and 3. It is evident that white women and children, older white men and negro women furnished the bulk of the cases. Pellagra is rare in the first year of life, fairly prevalent in white children under ten years of age, distinctly less prevalent at about the age of puberty, again increasing to maximum frequency in women in the age period sixteen to forty-five years, but remaining infrequent in men until after the thirty-second year. The greater prevalence in women during the active period of life is a most remarkable feature. The occurrence of pellagra in children of any district is a feature which stamps the district as an endemic focus of the disease.

The death-rate from pellagra in the initial attack is lowest in children and relatively quite low in women in the age period sixteen to forty-five years, indicating that the factors which bring about an attack of the disease are not identical with the factors which determine a fatal outcome of the attack. In children, pellagra would

appear to present no more serious danger than measles, while in both men and women more than fifty years of age the death-rate is well above 20 per cent. in the first year.

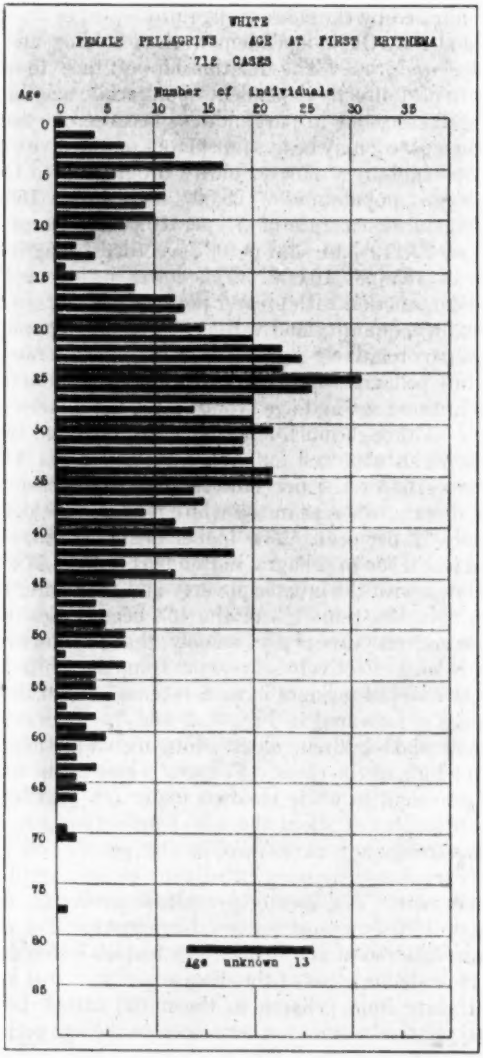

FIG. 1.—The age at onset of initial erythema in the 712 white female pellagrins of the Spartanburg County series. The age distribution is shown for 699 cases. In 13 cases the age was not ascertained. The small number of initial attacks from the eleventh to the sixteenth year is remarkable. (After Siler, Garrison and MacNeal.)

Relation to Food. The older theories assumed that pellagra is due to the toxic action of maize in the diet. It is undoubtedly true

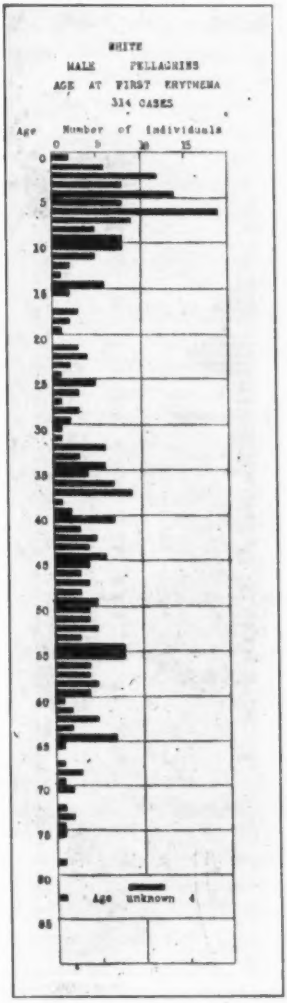

FIG. 2.—The age at onset of initial erythema in the 314 white male pellagrins of the Spartanburg County series. The age distribution is shown for 310 cases. In 4 cases the age was not ascertained. (After Siler, Garrison and MacNeal.)

that the vast majority of pellagrins have eaten maize or maize products, but feeding experiments with and without maize in

endemic foci of pellagra have failed to reveal any greater incidence of pellagra in those taking the large quantities of maize. Further-

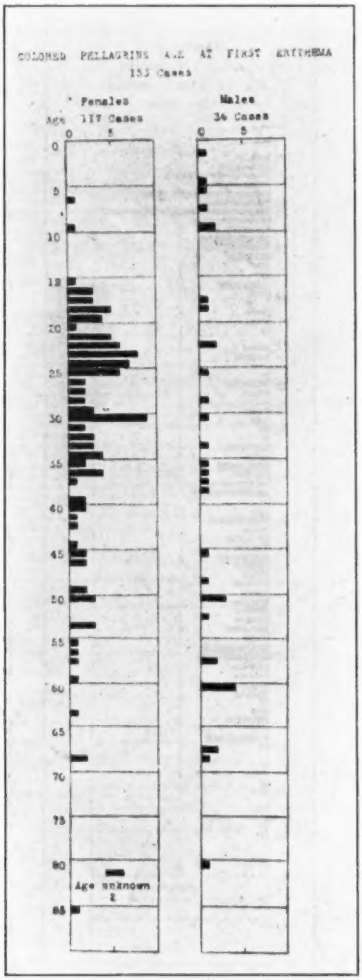

FIG. 3.—The age at onset of initial erythema in the 153 negro pellagrins of the Spartanburg County series. (After Siler, Garrison and MacNeal.)

more, the prophylactic exclusion of maize from the diet of pellagrous families has proved to be a failure, for under these circumstances there have been observed not only recurrences of the disease in those

already affected but also the outbreak of new cases in other members of the family. Perhaps even more convincing has been the report of Stannus of pellagra in prisoners who had had no maize for years, and of Viswalingham, who observed an outbreak of pellagra in Chinese coolies whose diet contained rice as the principal element and contained no maize. The Thompson-McFadden Commission, in 1913, failed to find a positive correlation between the frequency of use of any single food and the frequency of occurrence of pellagra. At present it would seem that no one seriously maintains that pellagra is caused by any single food. There remains, however, the possibility that the excessive use of certain foods, maize for example, may predispose to the development of the disease or render the attack more severe.

A second possibility is that the absence or insufficiency of certain dietary elements, rather than the excess of a certain element, may bear an etiologic relation to pellagra. The pellagra-preventing value of animal foods, especially milk, emphasized by the Illinois Commission and clearly demonstrated by the Thompson-McFadden Commission, is now generally recognized. Recently even Goldberger and his colleagues of the Public Health Service (1920) seem to have abandoned the advocacy of beans in favor of milk, milk products and fresh meat as preventive diet for pellagra. In my own opinion the relative pellagra-preventing value of these foods is similar to their value in preventing tuberculosis. They bring about improved nutrition and increased resistance to the specific cause of the disease. That the mere lack of animal foods is not the specific cause of pellagra is shown by the host of strict vegetarians who escape the disease. Furthermore, a relatively brief study in a pellagrous district suffices to disclose pellagrins who have taken milk daily all their lives, particularly young children, and occasionally one finds adult pellagrins who have eaten meat every day for years.

There remains a third possibility, namely, that general insufficiency of food may play an etiologic role. The theory that such insufficiency may be the specific cause of pellagra has already been discussed and rejected. There can be no question, however, that adequate nutrition is a most important factor of insurance against pellagra and in bringing about recovery from it, and that inadequate nutrition is a most important factor in predisposing to the development of pellagra in those who are exposed to the essential cause by residence in pellagrous districts.

Sanitary Disposal of Sewage. The association of poor sanitation with pellagra prevalence has been mentioned by many authors. The Thompson-McFadden Commission (1913) emphasized the fact that pellagra originates where insanitary surface privies are used and much less frequently where sanitary water-carriage systems of sewage disposal are properly employed. Such a relationship might

be explained by assuming that better sanitation increases the resistance to disease in general or that it operates by preventing the transfer of the specific cause of pellagra from the digestive tract of one person to another. An experimental test of this latter hypothesis was undertaken at Spartan Mills, S. C., in 1913, and the observations were carried through to August, 1916. Following, and apparently as a result of the installation of the sewer system, new cases of pellagra practically ceased to originate in the population of this village, whereas the old cases continued to suffer recurrences of pellagra about as would have been expected had no change in sanitation been undertaken. This relationship of sanitation to pellagra has been confirmed by the studies of Jobling and Peterson. The experiment at Spartan Mills has recently been attacked by Goldberger and Wheeler (1920), who state that they recorded 37 first-attack cases in Spartan Mills Village in 1917 (a year in which the original investigators were unable to continue their observations). The data to support this statement are referred to as "unpublished."

Experimental Inoculation.—Up to the present time the attempts to produce pellagra by experimental inoculation have failed in every instance to yield a conclusive positive result.

Clinical Manifestations and Course.

Introduction. Strambio described the signs and symptoms of pellagra in three stages of the disease. Roussel, although he did not follow Strambio's classification, nevertheless recognized three stages, not well separated from each other, which he designated as (1) commencing pellagra, (2) confirmed pellagra and (3) pellagrous cachexia. It seems to me preferable to regard pellagra as essentially a chronic disease presenting periods of activity and periods of quiescence, both of somewhat variable duration. According to this conception pellagra may best be studied clinically in two phases: (1) The period of active attack and (2) the interval between attacks. In the former period one may recognize a prodromal stage, an erythematous stage, a stage of hyperkeratosis and desquamation and a stage of sequelæ and convalescence. In the interval between attacks a great many various manifestations may be presented, some of them doubtless due to pellagra, but many of them depending upon quite other factors. The decision concerning the relative importance of pellagra and of other complicating disorders during this interval presents very great and often insuperable difficulties.

The Initial Active Attack. *Prodromal Period.* Pellagra sometimes begins suddenly with a cutaneous erythema as the first evidence of illness. More frequently there is a prodromal period varying from a few days to several months in length, during which

the patient is aware of diminished physical vigor; lessened appetite or distaste for particular foods or for all food, a burning sensation in the mouth and epigastrium, on the palms of the hands and the soles of the feet; attacks of vertigo, sometimes actual falling to the ground; depression of mind and spirit, evidenced by sadness and tardiness in thought, speech and action; pains in various parts of the body, especially headache, backache, pain and tenderness along the peripheral nerve trunks. Objectively there is often loss of weight, sometimes considerable; in women scanty or suppressed menstruation. Not infrequently there is diarrhea, more or less severe, but in many cases a persistent constipation or no evident disturbance of defecation. Reddening of the mucous membrane of the mouth and pharynx often accompany the burning sensation. Salivation is sometimes present. In patients carefully observed during this period one may occasionally detect an evanescent prelude erythema, first described by Merk. This eruption consists of numerous discrete red macules gradually fading into the surrounding skin, not raised above the skin surface and completely obliterated by slight pressure. It appears on the backs of the hands and forearms and may persist from a few hours to two or three days. This prelude erythema is probably not rare, but it is rarely observed. Pellagrin 597 of the Spartanburg series presented such a transient erythema on May 3, 1913, which disappeared in forty-eight hours and was followed by a frank and definite pellagrous eruption in June of the same year.

None of these prodromal symptoms or signs is sufficiently characteristic to warrant a certain diagnosis of pellagra, but the presence of many of them combined in the same individual in a pellagrous district is strong presumptive evidence of an impending attack of this disease, especially when a careful examination of the patient fails to reveal any other explanation of the observed manifestations. Even after the characteristic, diagnostic eruption subsequently appears, one is still left in doubt as to the relative importance of pellagra and of other complicating or predisposing factors in the causation of these interesting prodromal signs and symptoms.

The Stage of Active Eruption. The typical pellagrous eruption appears suddenly, ordinarily overnight, as a diffuse erythema or as separate red macules quickly becoming confluent, on the knuckles, dorsal surfaces of the phalanges and hands, gradually extending onto the wrists and forearms. At the same time or subsequently an eruption of similar character may appear elsewhere, especially on the forearms, the dorsal surfaces of the feet, the face, back of the neck, sternal region, upper arms, legs, perineum, scrotum, axilla and very rarely on the palms of the hands and the soles of the feet. Merk, who has presented the best clinical study of the cutaneous manifestations of pellagra, considers these eruptions in unusual locations, which he designated as "*atypische*," to be of no significance

for the diagnosis in the absence of the typical eruption on the backs of the hands.

The typical erythema is due to hyperemia, which causes not only redness but also swelling of the area above the level of the adjacent skin. The small flat areas, "fields," of the skin become more prominent while the furrows between the fields become deeper. As a rule the erythema becomes confluent within a few hours and then slowly extends, with a rather sharply demarcated margin. During this stage of progressive erythema the skin is very sensitive to external irritants, such as sunlight or even contact with the air. The sensation is that of burning. Itching may be complained of, but there is never any sign of scratching.

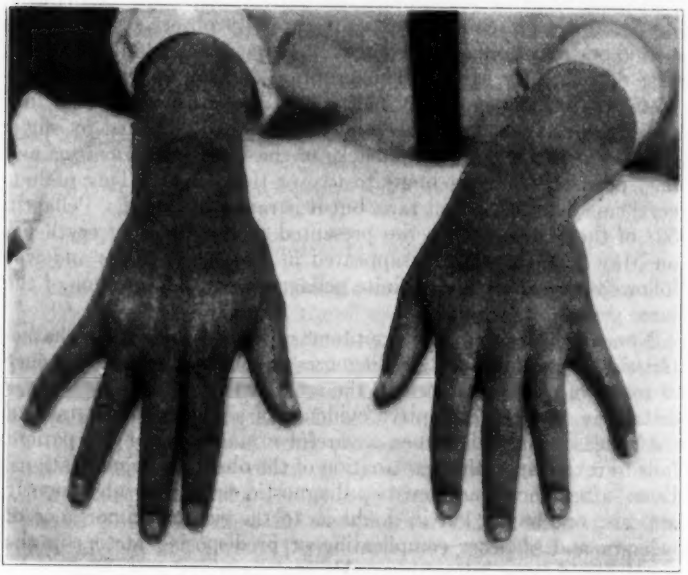

FIG. 4.—Typical pellagrous eruption in an adult male, in the stage of progressive erythema. (Photograph of the Thompson Pellagra Commission.)

Within the first few days the erythematous area begins to show increased desquamation in the form of fine scales, and in from one to two weeks the thickening of the horny layer of the skin with continuing desquamation obscures the underlying erythema. This hyperkeratosis becomes the most characteristic feature of the eruption during the greater part of its course. Thickening of the epidermis and desquamation continue for a variable period, two weeks to several months, usually about four weeks. In brunettes increased pigmentation also appears and is sometimes a marked feature of the erythematous area. Eventually the eruption tends

to disappear, the desquamation exposing a thin, parchment-like, smooth epidermis, more translucent than normal, with a pink, somewhat hyperemic dermis beneath. This restitution begins at the older parts of the lesion and gradually extends, so that the margins of the eruption persist longest. Indeed, in some patients one may observe at the same moment a narrow marginal zone of red, slowly advancing onto healthy skin, followed by a somewhat broader zone of deeply pigmented hyperkeratosis, this in turn succeeded by a still more extensive rough, scaly zone of desquamation, leading over into an area of atrophic smooth skin, where the eruption has completed its course. Occasionally one sees a new outbreak of erythema on the backs of the hands while there still remains the pigmented desquamating margin of a previous eruption on the upper forearms.

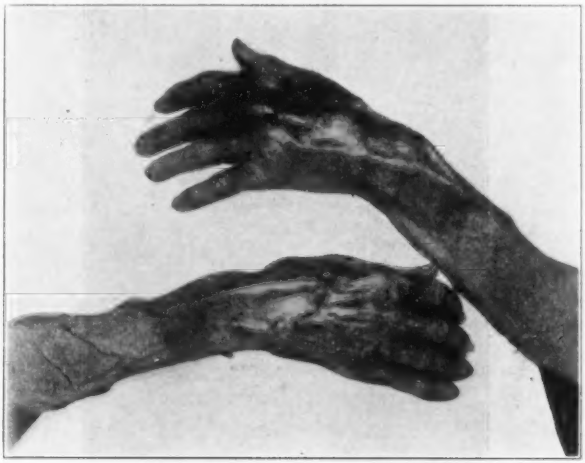

FIG. 5.—Pellagra in an emaciated woman, in the stage of hyperkeratosis and desquamation. (Photograph of the Thompson Pellagra Commission.)

The cutaneous eruption thus presents a variety of pictures in its various stages of evolution. In most cases the appearance is so characteristic that a reliable diagnosis may be made from a single observation. The subsequent developmental course of the eruption furnishes decisive evidence in most of the doubtful cases. In differential diagnosis one may have to consider trichophytoses and other forms of dermatitis due to local infection. These have undoubtedly been mistaken for pellagra at times, as recorded by Roussel. Their localization is hardly ever that of the typical eruption of pellagra. Sunburn may simulate the early stage of pellagrous erythema, but may be distinguished by its regular and

more rapid evolution. Scaly eruptions, which are occasionally observed on the forearms and shins of emaciated or cachectic individuals, may mislead the observer for a time. As a rule, however, the localization as well as the evolution of such eruptions will enable one to differentiate them from the eruption of pellagra.

The manifestations on the part of the digestive tract are variable in character, less constant in occurrence and far less reliable criteria for diagnosis than the cutaneous phenomena. Inflammation of the

FIG. 6.—Pellagra in a young woman in the stage of hyperkeratosis and desquamation. Emaciation is not evident. (Photograph of the Thompson Pellagra Commission.)

mucous membrane of the mouth and pharynx may precede, accompany or follow after the skin eruption. In degree this inflammation may vary from a slight reddening to a condition in which the entire visible mucous membrane is covered with a fibrinous exudate. Intense salivation is an occasional feature. Chronic pellagrins often present an irregularly swollen and fissured tongue. Swallowing may be so painful as to cause the patient to refuse solid food.

A burning sensation in the epigastrium, the pyrosis of pellagra,

is a fairly constant feature. It may precede the cutaneous eruption. Loss of appetite and actual distaste for food are frequently observed, nausea and vomiting only occasionally. In children, diarrhea usually precedes the eruption. In adults, particularly in women and in old men, diarrhea may be absent or may appear only late in the attack. Even in these patients, however, it may become a most alarming feature, the patient passing ten to thirty stools every

FIG. 7.—Pellagra in a child. The legs and feet show extensive eruption (Photograph of the Thompson Pellagra Commission.)

twenty-four hours for several days, with rapidly progressive emaciation and eventual lethal exhaustion. The stools possess a pronounced foul odor, often contain an excess of mucus and sometimes blood. Rectal examination frequently reveals a reddened mucous membrane resembling the redness of the mouth and pharynx. The alimentary disturbances may accompany the skin eruption or may appear, persist or disappear in a way quite independent of the latter. At times an exacerbation of the skin lesions is associated with an

improvement in the alimentary symptoms, and *vice versa*. This is probably mere accident, but some patients state that they always feel better when the eruption has appeared on the hands.

Nervous and mental disturbances are very rare in children but rather common in adults. Symptomatic depression is a frequent early manifestation. Vertigo and actual falling from loss of equilibrium are emphasized as early symptoms by Roussel. In the United States, Singer has found vertigo a prominent early symptom in six of eighteen severe cases. The more pronounced and characteristic nervous manifestations may be considered under two headings, (1) the so-called pellagrous insanity and (2) a peripheral neuritis.

The mental disturbance is either a frank toxic psychosis or one of the usual types of mental disorder varying according to the psychologic make-up of the individual, evidently precipitated by a toxic influence. Mental disturbance is observed in about 40 per cent. of all cases of pellagra, most frequently in women in the age period forty-one to sixty years and in men in the age period twenty-one to forty years. Children are practically exempt. Singer found that about 95 per cent. of the mental disorders appear to be the direct result of the pellagrous intoxication, corresponding to similar mental disturbances in other diseases and not properly to be classed as insanity. Symptomatic depression is the most frequent mental change, and it has been designated as the neurasthenic type. The attitude is that of a more or less hopeless sadness, with a lowering of tone, energy and attention, varying to melancholia, sometimes of a religious type, occasionally with suicidal tendency, to clouding of perception, sense falsifications, stupor and, in the most severe cases, to a syndrome of central neuritis leading to death. In other instances the picture is that of delirium, not essentially different from that of typhoid fever or of pneumonia. In most instances the depression or delirium clears up as the other manifestations of pellagra disappear and physical strength is regained. In about 5 per cent. of the mental cases Singer found a picture corresponding to one or the other of the well-known types of mental disorder, such as manic-depressive, hysteric, dementia precox type or senile dementia. In these cases the attack of pellagra appears to serve as the precipitating cause, which brings out a mental disorder already existing in the patient. During the active pellagrous attack the type of mental disorder may be masked by depression or delirium, but as recovery from pellagra takes place the characteristic features of the individual's preëxisting psychosis become clearly evident. Such patients present actual insanity, but the causation of it is not properly ascribed to pellagra. It would seem, however, that individuals of faulty nervous organization are relatively predisposed to pellagra and that an attack of pellagra tends to make evident the defective nervous organization

of such individuals. Chronic insanity due to pellagra itself, if it occurs at all, is rare.

The peripheral neuritis most frequently manifests itself as a paresis or paralysis of the muscles of the lower extremities. This occurs in children as well as in adults, but is not at all common and may really be due to some accompanying or complicating disease. It resembles an alcoholic neuritis and has been diagnosed as such in some cases. Possibly continued large doses of arsenic may occasionally bear a causal relation to the neuritis.

The temperature is characteristically subnormal in pellagra, varying from 35.5° to 37° C. Frequently it rises rapidly to 39° C. or even higher in the two or three days preceding death.

The pulse-rate is usually high in relation to the temperature and the pulse frequency usually increases sharply along with exacerbation of the other symptoms. The blood-pressure is low.

Duration of the Attack. The usual mild attack of pellagra lasts about four weeks from the appearance of the erythema until the manifestations are no longer evident. In some instances a second attack may supervene before the eruption of the first has entirely vanished, or, without intermission, the hyperkeratosis and desquamation may continue unabated for several weeks or months in exceptional cases. There is a very evident tendency to self-limitation of the attack, but the course and duration are subject to considerable variation and appear to be influenced to some extent by rest, careful feeding and nursing and especially by a diminution in the temperature of the atmosphere. Cooler weather or removal to a cooler climate stands out as perhaps the most definite factor in cutting short the pellagrous attack.

TABLE I.—DISTRIBUTION OF DEATHS IN THE FIRST ATTACK OF PELLAGRA ACCORDING TO YEAR OF ONSET IN SPARTANBURG COUNTY, SOUTH CAROLINA.

Year.	Before 1908.	1908.	1909.	1910.	1911.	1912.	1913.	1914.	Total.
Incident cases . .	57	20	57	141	234	211	251	209	1180
Deaths	13	2	16	28	33	27	38	30	187
Death-rate per cent.	22.8	10.0	28.1	19.9	14.1	12.8	15.1	14.4	15.8

Death-rate. The death-rate in the first attack in the 1180 recorded pellagrins of Spartanburg County up to 1915 is shown in Table I. The average indicated death-rate, 15.8 per cent., is not very different from that of the later years. It may be regarded as an approximate indication of the death-rate in the first attack of pellagra.

The relationship between death-rate in the initial attack and the race, age and sex of the patients has been studied in these same

statistics. This death-rate in the 1027 white pellagrins was 12 per cent. and in the 153 negroes it was 41.8 per cent. Searcy's earlier report showed a death-rate of 64 per cent. in pellagra among the colored insane. Lavinder's statistics for Mississippi up to 1913 showed a death-rate of 29.2 per cent. in negroes and 11.4 per cent. in white pellagrins. Pellagra may therefore be regarded as distinctly more fatal to the colored race.

In respect to age and sex the Spartanburg County statistics show 14 cases of pellagra at an age of less than two years, 5 white girls, 8 white boys and 1 colored boy, in the total 1180 cases. Of these only one, the colored boy, died in the first attack. Including these infants there were 212 cases in children under twelve years, 99 white boys, 104 white girls, 1 white child of unknown sex, 2 colored girls and 6 colored boys. Of these there died in the initial attack 2 white boys, 3 white girls and 2 colored boys, a total of 7, or 2.5 per cent. In the age period twelve to sixteen years there were only 21 initial attacks of pellagra, 9 in white girls, 11 in white boys and 1 in a colored girl aged fifteen years. Only one of these died in the year of onset, a white girl, aged thirteen years. The low incidence of pellagra in these four years is in marked contrast to the incidence in younger persons of both sexes and to that in older women. In the age period sixteen to twenty years the death-rate in initial attack was 6.7 per cent. in 45 white women, zero in 6 white men, 46.7 per cent. in 15 colored women and 50 per cent. in 2 colored men. The analogous death-rate in each decade after age twenty is shown in Table II. From this table it is evident that pellagra is much more

TABLE II.—DEATH-RATE IN YEAR OF ONSET BY DECADES AFTER AGE TWENTY YEARS.

Decade.	20–29.	30–39.	40–49.	50–59.	60–69.	70–79.	80–89.	Total.
White women	4.6	9.8	14.9	31.8	47.6	33.3	..	11.9
White men	16.7	20.0	15.9	24.5	21.7	37.5	100.0*	21.2
Negro women	31.0	43.3	63.3	40.0	66.7	..	0.0*	40.2
Negro men	33.3	50.0	0.0	50.0	71.4	..	100.0*	50.2

* Only one case in each instance.

fatal in its initial attack in the negro race and in males, precisely those groups least frequently attacked by the disease in the population studied; furthermore there is a clear indication of increased death-rate with increased age. The benign character of the disease in children is especially noteworthy.

The Interval after the Initial Attack. Subsequent to the initial attack the patient may again become quite fit. There is ordinarily a distinct gain in weight and in some a rather striking gain. The patient frequently refuses to believe that his attack could have been any such serious disease as pellagra. In nearly half the cases,

however, there remains even at this time evidence of depressed vitality, weakness, diminished body weight, diminished or absent menstrual flow in women. As a rule the vast majority of pellagrins improve as colder weather comes on and all but a very few appear quite well in the winter. A few remain weak, cachectic or mentally deranged; rarely one continues with diarrhea and cutaneous eruption into the colder season. These latter usually die in December, January or February. Even in a pellagra focus containing hundreds of cases it is ordinarily impossible to demonstrate the characteristic manifestations of the disease in a single case in mid-winter.

The interval of freedom from pellagra may be prolonged indefinitely so that the patient may be considered to have recovered. This is a common result in institutional outbreaks, where a large number of individuals may be attacked at one time and, subsequently, probably as a result of more liberal dietary and improvement in general hygiene of the institution, the disease may promptly and finally disappear.

In the general population of Spartanburg County, 681 pellagrins who survived the year of onset showed 482 with recurrence and 199 free from recurrence the following year, a recurrence rate of 70.8 per cent. Of those who suffered recurrence in the second year 63 died. Of the survivors 292 were followed through the third year, and of them 228, or 78.1 per cent., had recurrences. Of those who survived attacks in the first, second and third years 78.6 per cent. suffered recurrence in the fourth year and in the fifth year the recurrence rate for those with four previous annual attacks was 76.2 per cent. It would appear that when the habit of recurrence has become established it has a strong tendency to continue. On the other hand those who have escaped from recurrence for one or several years may nevertheless subsequently suffer recurrence. Thus of 137 pellagrins who survived the second year without recurrence, 16 suffered recurrence in the third year, 106 remained free from recurrence and 15 were of uncertain record. Of 62 individuals who had passed two years without recurrence, 11 suffered recurrence in the fourth year of the disease (17.7 per cent.). After three years without recurrence, 13.3 per cent suffered recurrence in the fifth year. Indeed, apparently reliable records in one case indicate a recurrence after nineteen years of freedom from recognizable manifestations of the disease.

It is evident that one should be guarded in stating that any patient has recovered from pellagra. It would appear wiser to speak of the disease as arrested or as quiescent, as is now the rule in tuberculosis.

The Recurrent Attack.—The recurrent attack of pellagra resembles in its clinical features the initial attack. On the average, recurrent attacks appear about two weeks earlier in the season than do the initial attacks of that same year. Recurrences are, on the average, milder than the initial attacks and the death-rate is correspondingly

lower. Thus in the Spartanburg County series the total recorded recurrent attacks number 1053 with 130 deaths, or 12.3 per cent. In the same series the death-rate in initial attack was 15.8 per cent. This observation is contrary to the oft-repeated statement that the prognosis as to life is good in the early stages but bad in the late stages of the disease. It is, however, in accord with the general observation that the severe, fulminant cases of pellagra are more frequent in those places where the disease has recently appeared and are rare in districts where it has been endemic for a long time.

In the Spartanburg County series the total instances of escape from recurrence for a year were 617 and the total number of recurrent attacks 1053, the ratio being approximately 4 to 7. The tendency to recurrence depends to a marked degree upon age and sex. This is shown in Figs. 9 and 10. Of 12 white girls under fifteen years of age, with onset of pellagra in 1911, only 6 were known to suffer recurrence in 1912, 4 in 1913 and 3 in 1914. In

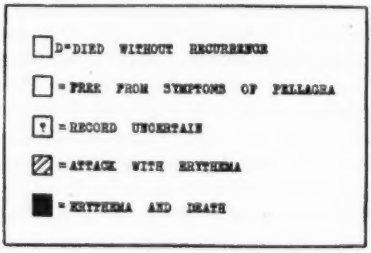

FIG. 8.—Key for interpretation of Figs. 9 and 10. (After Siler, Garrison and MacNeal.)

1914, six remained free from recurrence. Two had passed from observation after 1911 and one had died in 1912 without recurrence of pellagra. The 25 white boys under fifteen years of age with onset of pellagra in the same year show an even more striking recovery rate. Of these 12 escaped recurrence in 1912 while only 8 are known to have suffered recurrence. In 1913 these numbers were 17 and 3 respectively, and in 1914 they were again the same. At the end of four years these 37 children, boys and girls, showed only 6 with known recurrent attack in the fourth year, while 23 escaped recurrence in the fourth year (1914) and 22 were free from signs of the disease in both 1913 and 1914. In the four years there had been only one death in the group, from dysentery, apparently not pellagra. From these and other similar figures it would appear that pellagra is not more serious for children than is measles.

Jobling and Peterson have shown that child pellagrins are of average weight, height and age development until the disease has recurred for some years, when the little pellagrins are somewhat

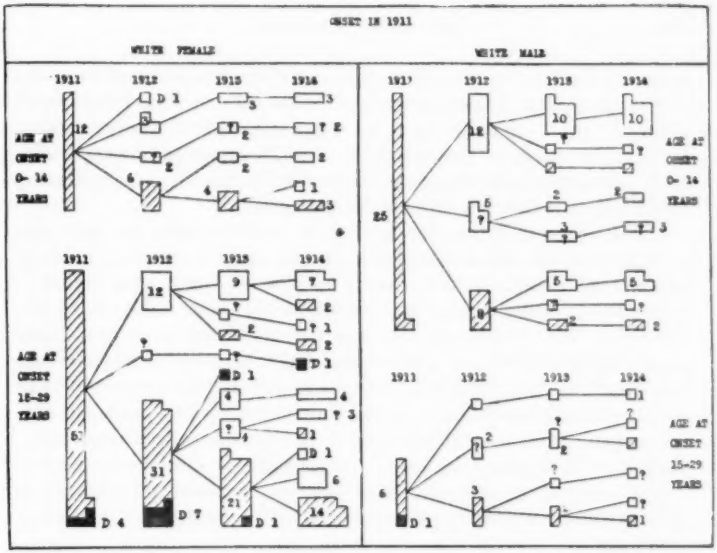

FIG. 9.—Subsequent behavior of white pellagrins of the Spartanburg County series who suffered initial attack in 1911 before attaining the age of thirty years, grouped according to sex and age at onset. Note the absence of deaths in the groups under fifteen years of age and the numerous recoveries in these groups. (After Siler, Garrison and MacNeal.)

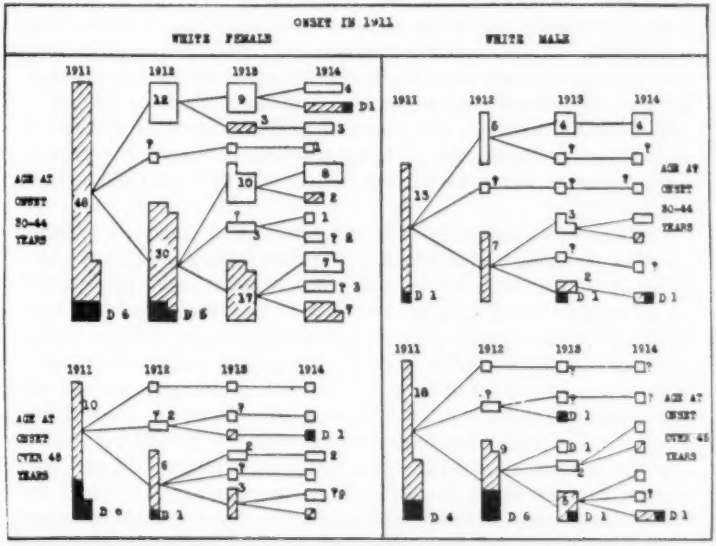

FIG. 10.—Subsequent behavior of white pellagrins of the Spartanburg County series who suffered initial attack in 1911 after attaining the age of thirty years, grouped according to sex and age at onset. Here deaths are more numerous and apparent recoveries less frequent. Note the recurrences after two years of freedom from attack. (After Siler, Garrison and MacNeal.)

below the average. Possibly this retarded development may be due to the pellagra, but there remains also the possibility that these children may be handicapped by some other abnormality, so that they fail to outgrow the disease as does the average normal child, their subnormal development depending upon this complicating abnormality rather than upon the pellagra.

While these children did so well it is interesting to note the behavior of the older pellagrins in the same community, blood relatives of these children, chiefly members of the same families, living in the same houses and eating at the same tables with the children. The women in the age period fifteen to thirty years numbered 55 in 1911. At the end of 1914, 17 were living free from recurrence in the fourth year (1914), 19 suffered recurrence in 1914 and 14 had died of pellagra in the four years. The 7 males in this age group (fifteen to thirty years) are hardly worth discussing. Only 3 were followed in 1914, and of these 2 suffered recurrence and 1 escaped recurrence. The older age groups of both sexes show a similar tendency to recurrence with a death-rate increasing in old age.

Relation to Pregnancy and Childbirth. Pregnant women are relatively less frequently attacked by pellagra, and if the disease appears in them it tends to run a milder course. Thus in our series there were only 20 instances of initial pellagrous attack during pregnancy; 18 recovered, 1 died of pellagra six weeks after parturition and 1 continued in poor health after the child was born in August, 1912, and died of pellagra in September, 1913. Pregnancy bears a similar relationship to recurrent attacks of pellagra. Thus of 79 instances of pregnancy in known pellagrous women, in only 17 instances was a recurrence of pellagra observed during the pregnancy, a recurrence rate of 21.5 per cent. in pregnant women as compared with an annual recurrence rate of 63 per cent. for women in general.

In the months following childbirth women are relatively predisposed to pellagra, both initial and recurrent attacks. In our series 53, or 10.1 per cent., of the pellagrous white women suffered the initial attack of pellagra within six months after the birth of a child. In an analogous manner pellagrous women suffered recurrence of the disease with excessive frequency in the first three months following childbirth, no less than 21, or 24.7 per cent., of the 85 pellagrous white women suffering recurrence in these three months. This rate may be compared with the annual recurrence rate of 63 per cent. by dividing the latter by 4, giving 15.8 per cent. for the average three months period for all women. When the childbirth occurred in the period January to April, inclusive, no less than 50 per cent. of the pellagrous mothers suffered recurrence within three months; when the childbirth occurred in the period September to December all the pellagrous mothers escaped recur-

rence in the following three months. This seasonal relationship should be given attention in the management and care of pregnant women threatened with pellagra.

Pathologic Anatomy. *The Cutaneous Lesions.* Merk has published the most thorough description of the skin lesions as they appear clinically. Unfortunately his work did not include histologic studies. Griffini appears to have been the first to describe the microscopic appearance of the skin. In the desquamative stage he observed a hypertrophic horny layer, with evidence of abundant scaling and excessive productivity in the rete Malpighii. In another case, in the stage of "anemia," he found sclerosis of the bloodvessels of the cutis, more particularly of the papillæ. A third case was examined at the atrophic stage. In this one Griffini found sclerosis of the deeper cutaneous vessels and of the connective tissue of the corium, a frank atrophy of the horny layer and little reproductive activity of the rete Malpighii. The sweat-glands, hair follicles and sebaceous glands seemed not to be abnormal.

P. Raymond studied the skin from the back of the hand of a chronic pellagrin in the atrophic stage. The epidermis as a whole was thinned but the horny layer was thickened absolutely as well as relatively; the papillæ were smoothed out. The horny layer and the rete Malpighii were of equal thickness and the former showed numerous clefts, indicating active desquamation. Hyperkeratosis was a most prominent feature. The stratum granulosum was composed of thin, elongated cells in which eleidin granules could not be distinguished. The rete was atrophic, showing reduction in both number and size of cells. Many of the nuclei had undergone a vesicular degeneration, which Raymond considered to be evidence of irritation in response to vascular dilatation in the corium. The basal cells contained abundant pigment. The papillæ had vanished entirely and the boundary between the ectoderm and the mesodermal layer was represented only by a slightly toothed band. In the corium there were large vascular tufts, the large volume of which contrasted sharply with the atrophic epidermis. The hair follicles, sweat-glands and particularly the nerves were unchanged. The elastic and collaginous fibers appeared normal except for moderate thickening of the latter. In summary, Raymond designates hyperkeratosis and atrophy of the rete as the essential cutaneous changes of pellagra.

Babes and Sion appear to have studied the skin in various stages of the disease. They mention the various features of pellagrous skin lesions, including secondary infections which take place, but these descriptions are inferior to Raymond's in respect to clearness. Babes and Sion mention a moderate diminution in the myelin of the cutaneous nerves as well as the presence of rod-like structures in the corium, suggesting bacteria. They found sebaceous glands containing bacterial colonies and surrounded by granulation tissue,

in which hyperplastic endothelial cells and plasma cells were abundant.

Ormsby and Singer, after study of a large number of sections of pellagrous skin, designate the general picture as that of an angioneurotic process resembling that seen in multiform erythema. They observed thickening of the horny layer, the stratum granulosum and rete being practically normal; edema and cell infiltration

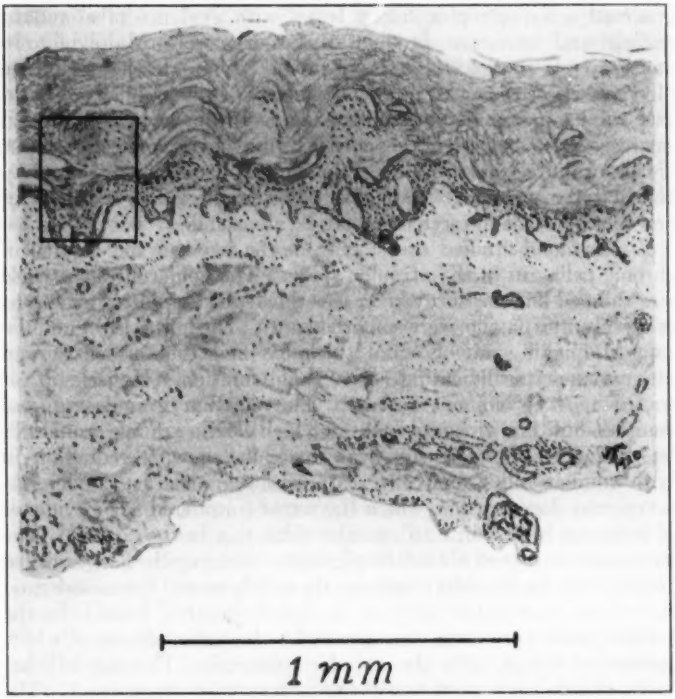

FIG. 11.—Section of skin with mild pellagrous eruption in the stage of hyperkeratosis from a woman aged twenty-nine years; stained with hematoxylin and eosin and drawn with aid of the camera lucida. The horny layer is greatly thickened and shows active desquamation with scattered areas of parakeratosis. There is edema of the corium, especially of the papillary part.

of the superficial part of the corium, especially the pars papillaris. Upon study with the high power the hyperkeratosis was seen to be well marked, with areas of parakeratosis here and there. Many pigment granules were present. The rete was practically normal except in places where its integrity was interfered with by infiltrating cells. In the papillary layer cellular infiltration was quite marked, particularly in the vicinity of bloodvessels. The collagen showed

edematous changes. Deeper parts of the corium appeared normal. No microörganisms were found.

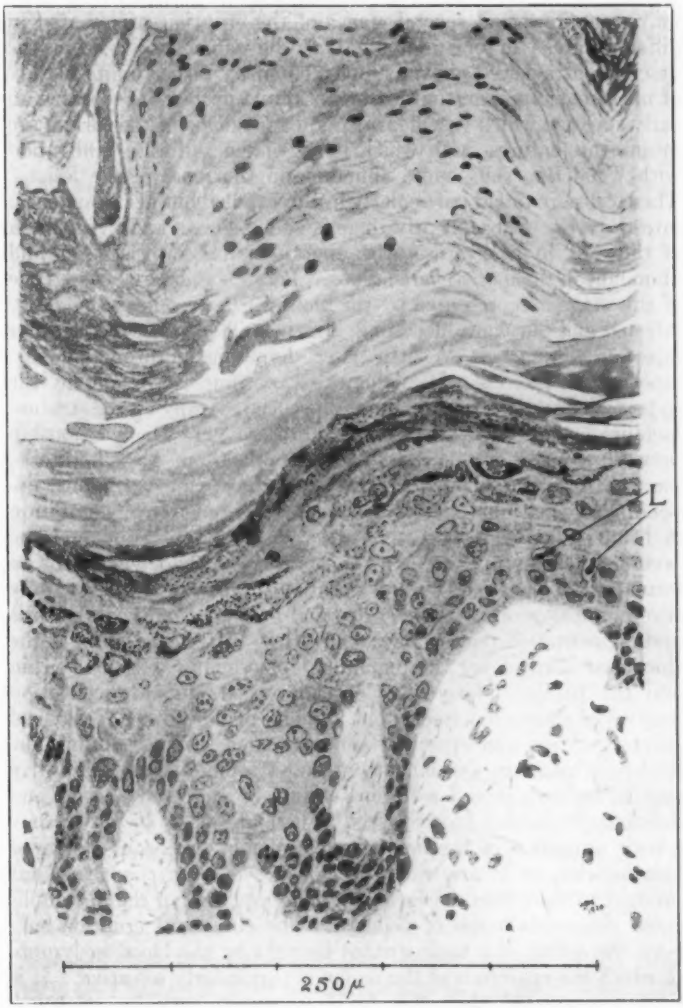

FIG. 12.—A portion of the same section, the location of which is indicated by the black outline in Fig. 11, more highly magnified; camera lucida projection, Zeiss obj. 4 mm., oc. 4. Active desquamation is indicated by the clefts in the horny layer and parakeratosis by the many nuclei in this layer. The stratum lucidum contains numerous brown pigment granules. The regularity of the stratum granulosum is disturbed and the lymph canalicular system of the rete Malpighii is moderately distended by edema. Increase of wandering cells is only slight. At *L* are leukocytes.

An adequate description of the cutaneous lesions of pellagra will require a consideration of all the various stages of the eruption, with a correlation of the gross and microscopic appearances. One may sometimes find several stages of the eruption represented in different areas in one individual at the same time. From the description reviewed above, supplemented by rather limited study of microscopic preparations, it seems to me proper to recognize an early stage, in which vascular injection and edema of the corium are prominent features, with which is associated a diffuse infiltration with wandering cells, more abundant in the more severe lesions. These cells are found particularly in the papillæ, but also wander up into the rete. Subsequently there is added edema and hyperplasia of the rete, hyperkeratosis with spots of parakeratosis, large and abundant in the more severe lesions. Perhaps the most severe type of this stage is represented by the bleb, which becomes secondarily infected and purulent, ulcerated. In the milder forms the vascular injection diminishes. A little later, hyperpigmentation appears, especially in the rete. Hyperkeratosis continues and gradually the hyperpigmentation becomes more superficial, occupying the stratum lucidum and deepest strata of the horny layer. The relationship between congestion, edema, cellular infiltration, hyperkeratosis, parakeratosis and pigmentation is subject to wide variations, depending in part upon individual peculiarities (greater pigmentation in brunettes) and in part upon the rapidity of evolution and the severity of the eruption. An exaggeration of the edema leads to formation of blebs and ulcers, eventually purulent. Less acutely severe eruptions are relatively dry and in these the hyperkeratosis and pigmentation tend to be exaggerated. After exfoliation of the thickened horny layer the remaining epidermis is abnormally thin and the papillæ relatively smoothed out. Complete restitution may occur after a few weeks, but in many instances after prolonged severe eruption and especially after repeated severe eruptions the epidermis remains permanently thin, atrophic, with diminutive papillæ beneath it and a fibrous corium of increased density and deficient in smaller bloodvessels. There seems to be no characteristic alteration of the nerves, sweat-glands, sebaceous glands or hair follicles, or at any rate the evidence of such changes so far brought to light does not establish them as a part of the uncomplicated cutaneous lesion of pellagra. The cutaneous eruption suggests the action of a toxic irritant brought by the blood or lymph, to which the epidermis of the region is particularly sensitive. It is further suggested that this toxic substance may be relatively inactive until it has been changed at the site of the lesion by peculiar ferments of the epithelial cells or possibly by the accessory influence of diffuse or direct sunlight.

The Nervous Lesions. These also require to be considered in relation to the stage of the disease. The earlier observations of

Tuczek would seem to deal rather with the late after-effects of numerous attacks of pellagra if not actually with results of other complicating diseases. More recent studies, particularly those of Mott and of Singer, have brought into prominence the structural changes in the ganglion cells themselves throughout the brain, spinal cord and spinal ganglia. In a rapidly fatal initial attack of

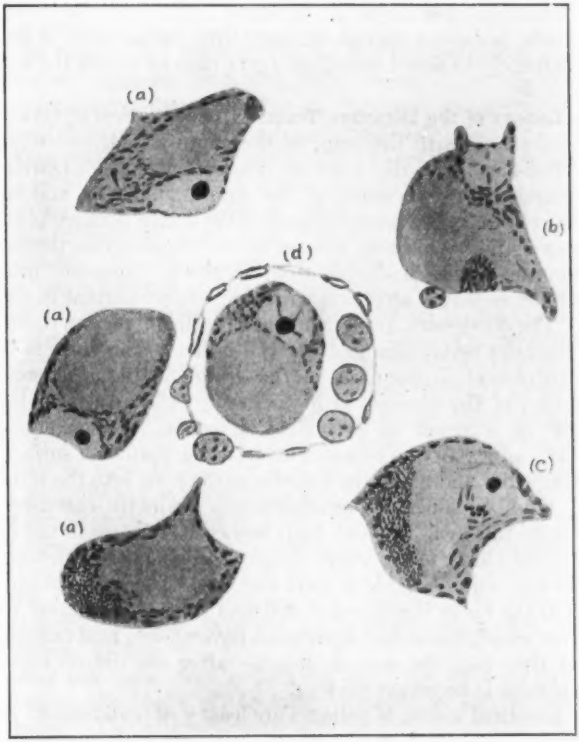

FIG. 13.—Nerve cells showing chromatolysis and pigmentary changes. (*a*) From Clarke's column; (*b*) from anterior central convolution; (*c*) from anterior cornu in cervical region; (*d*) from posterior root ganglion. From a woman, aged forty-three years, dying in the initial attack. (After Singer.)

pellagra, Singer found the most pronounced changes in the Betz motor ganglion cells of the cerebrum and in the cells of Clarke's column in the cord. Fiber degeneration was found diffusely scattered throughout the white matter, not especially involving the pyramidal tracts and not abundant in any tract. Degenerated fibers were also found in both the anterior and posterior spinal roots. The glia cells were perhaps increased around some of the larger

bloodvessels and in places the cerebral vessels showed some increase of adventitial nuclei, but no infiltration of the perivascular sheaths, a striking contrast to the pictures seen in syphilis and in trypanosomiasis. In more chronic cases the increase in glia cells about the bloodvessels was more definite and quite marked in some instances, and the vessels themselves were thickened. The nerve lesions, like the cutaneous changes, indicate the action of a diffusely distributed toxic substance in solution in the blood and lymph, for which the nerve cells possess, a special susceptibility, rather than a formed, more definitely localized infectious agent present within the nervous tissues.

The Lesions of the Digestive Tract. In the alimentary tract also the lesions vary with the stage of the acute attack and represent only after-effects in the interval between attacks. During life the inflammatory hyperemia of the mouth, pharynx and of the rectum are often prominent features of the active pellagrous attack. Autopsy at this stage nearly always shows inflammation throughout the intestine, patchy in distribution. Strips of hyperemic intestine several feet in length alternate with strips fairly normal in appearance. The duodenum, lower ileum, caput coli and rectum commonly show the most severe changes. In the earlier lesions there is vascular engorgement, hyperplasia of the lymphoid tissue, edema and infiltration of the mucosa with wandering cells. In later lesions, possibly as a result of secondary infection, moderately dense collections of wandering cells extend from the epithelial surface into the submucosa and along the vessel sheaths even into the muscular coats. Loss of superficial epithelium is evidently extensive, for even in the milder lesions one finds numerous mitoses in the crypts and, in the older, more severe lesions the glands are deficient in number and quite variable in form and size. Ulceration commonly occurs in the lower ileum, caput coli and rectum, and these ulcers, which are small, round and superficial, nevertheless heal only slowly, so that they may be seen at autopsy after the diffuse intestinal inflammation is no longer evident.

The intestinal lesions of pellagra are least well understood. Some authorities (Roussel) regard them as entirely trophic and dependent upon antecedent changes in the nerves. Others regard them as an expression of direct toxic action on the intestinal wall by the essential poison of pellagra during its absorption. Doubtless the normal intestinal microörganisms also play a part, particularly after ulceration has occurred. A clear understanding of the intestinal lesions will doubtless have to await a better understanding of the etiology of pellagra itself.

Pathologic Chemistry. Myers and Fine found the gastric juice of pellagrins often deficient in hydrochloric acid and not infrequently in pepsin also. The feces contain, as a rule, a markedly abnormal excess of indol and skatol. The urine commonly shows a

trace of albumin and a few tube casts and in most cases a distinct test for indican. At times indican is present in enormous amount. These findings all point to a gastro-intestinal derangement and profound bacterial decomposition in the intestine. Metabolism studies on pellagrins have shown that these patients possess normal ability to utilize the food principles. In fact the utilization was surprisingly high, considering the evidence of local gastro-intestinal derangement.

Bacteriology. The work of Tizzoni and his associates, who have isolated an organism from the blood which they regard as the cause of pellagra, may probably be dismissed as unreliable. The intestinal flora is certainly profoundly altered in pellagra. There is a large increase in the variety of microbes present in the feces as compared with the normal as well as a disturbance in the numerical relationships of the normal types. Further investigations in this field of work are much to be desired.

Diagnosis. The diagnosis of pellagra has to be made by observation of the symptoms and signs presented by the patient, and this diagnosis may be supported by demonstration of the typical anatomic changes in the tissues. Accessory facts may be utilized to some extent. Of these, perhaps the most important is a history of having lived in a pellagrous district. Some authors attach great importance to a history of having eaten maize, even going so far as to exclude pellagra absolutely if maize has not been eaten (Roussel) or even to assume that all persons who habitually eat maize actually suffer from pellagrous intoxication in a mild form. These conceptions are not in accord with observations on pellagra in the United States. Some authors appear to attach considerable importance to emaciation and physical weakness as evidence of pellagra, but these manifestations are common to so many pathologic conditions that comment upon their diagnostic value is superfluous.

Among the signs and symptoms, only the typical cutaneous eruption on the backs of the hands warrants a definite diagnosis of pellagra. This eruption bears the same relation to the diagnosis of pellagra as does the eruption of smallpox or measles to the diagnosis of those diseases. In the recognition of the pellagrous eruption, its localization on the backs of the hands, approximate bilateral symmetry, sudden appearance as an erythema, gradual evolution to hyperkeratosis, with or without hyperpigmentation, the subsequent desquamation and final restitution are important. A dermatitis due to molds may simulate this eruption in appearance, but such a dermatitis usually occurs elsewhere than on the backs of the hands. Roussel, however, mentions cases in which the differential diagnosis was finally made only by the microscopic demonstration of mycelial threads in lesions on the backs of the hands. The beginning and developmental course of a mold derma-

titis is usually different also, so that continued observation may alone suffice for its recognition.

A tentative diagnosis of pellagra is often justified without observation of the eruption. Certainly the disease is usually still present after the acute attack and the eruption have disappeared and there is abundant evidence that the patient suffers from the disease in the absence of the eruption. However, such a tentative diagnosis should be abandoned if the patient does not subsequently present the eruption or confess to its earlier presence.

Prophylaxis. The practical prevention of pellagra has to be based upon a knowledge of etiology. The measures may be grouped in two classes: (1) Those measures which enhance the individual resistance to the disease, and (2) those which diminish or exclude the opportunity for the causative factor or factors to attack the individual. First, in regard to individual resistance: it is evident that even in its endemic centers pellagra attacks only a small proportion of the population at any one time. Those who are physically vigorous escape to a very large extent and therefore the maintenance of robust physical vigor is an excellent insurance against pellagra. The nature of human existence, however, is such that in every natural community of families there will be some tender young children, some children occasionally sick with measles, whooping-cough or gastro-intestinal derangement, some women in the puerperium and some old people in the decline of life when robust vigor naturally wanes. Therefore, although the maintenance of individual resistance at a high level offers much, it nevertheless has its limitations. In regard to the second class of measures, which diminish the opportunity for the cause to reach the individual, opinion is much less settled. Most effective is distance from persons suffering from the disease. When pellagra has prevailed among the general population new cases may be expected to continue to appear. In the United States the disease numbers its victims by the thousands every year in some states while in others it is either wholly unknown or is recognized as a rare disease of transient visitors from pellagrous districts. Even in its endemic areas, large districts remain relatively free from the disease while in other parts from 5 to 10 per cent. of the people are pellagrins. Avoidance of the endemic centers becomes, therefore, an evident means of avoiding pellagra. However, even in the small villages most severely afflicted, those people who live farther away than next door from the residence of a pellagrin are less liable to contract the disease than those who live next door to or in the same house with such sick persons.

Sanitary disposal of the human wastes of a community would appear to be one of the most important factors in preventing the occurrence of new cases of pellagra. Physical equipment such as sewers, a piped water supply and screens are evidently important,

but sanitary instruction, and especially adequate inspection service to insure the proper use of the equipment, must not be neglected. Lunatic asylums, provided throughout with the most approved sanitary appliances, still have their "untidy wards."

General improvement in nutrition, and particularly the liberal consumption of milk and of wholesome, fresh meat, certainly plays an important part in preventing pellagra, not alone among those who have not yet contracted the disease but also in preventing recurrences in those already affected by it. It is probable that such foods act by enhancing the general vigor and thus increasing resistance of the individual to the disease, but many investigators believe that these foods have a more definitely specific action by relieving a supposed specific deficiency or supplying a necessary vitamine in the diet.

Treatment. The treatment of pellagra offers two phases for consideration: (1) The management of the case during the acute attack of the disease, and (2) the management of the patient after recovery from the attack. As we have seen, recovery from the attack occurs in about 85 per cent. of instances. In fact, about half the attacks do not cause the patient to go to bed and the vast majority run their course to recovery without any definite treatment. In those who do become bedridden the death-rate is fairly high.

Bearing in mind, therefore, that the attack tends to self-limitation the indications are for supportive and symptomatic treatment. A comfortable bed in a clean, pleasant and moderately cool room, with a competent, interested and sympathetic nurse, almost ensure recovery. The lips, mouth, teeth and pharynx should be kept scrupulously clean. Irritation of the eruption is lessened by bandaging with an ointment of zinc oxide, lanolin and vaselin. The diet should be liberal and should include milk as the principal element. Every effort should be made to encourage the appetite, but overfeeding to the point of distaste or nausea is dangerous. In severe cases food may sometimes be refused entirely for as long as three days, with subsequent return of appetite and eventual recovery. Pellagrins are very susceptible to suggestion and the presence of recovered patients has a real therapeutic value. Conversely, a pellagrin, surrounded by friends or by nurses who regard the disease as horrible and necessarily fatal, usually dies. Probably the psychical state influences directly the nutrition and indirectly the outcome of the attack.

Pustules, fissures, ulcers and extensive sloughs of the skin require mild antiseptic wet dressings. The diarrhea had best not be intefered with, and it is not a contra-indication to a liberal milk diet. Peripheral neuritis and paresis require massage, passive movements and elevation of the bed-clothing from the feet in chronic bedridden cases. Mental derangement should be expected in all severe cases, and it requires intelligent, sympathetic treatment.

Physical restraint usually aggravates the difficulty. Of the hypnotics, probably chloral is most effective and least objectionable. Morphin is not recommended. Mental cases require vigilance, for there is a real suicidal tendency in some. The noisy delirium of these patients makes their treatment in a general hospital very difficult.

Complicating disorders should be carefully looked for. Often their importance quite overshadows that of the pellagra itself. In a tuberculous pellagrin treatment of the tuberculosis is the pressing indication. Chronic alcoholism and its sequelæ, and, in women, pelvic disease, are common complications of pellagra and require their special consideration. In institutional pellagra, undernourishment from prolonged lack of adequate food is common, and it is one of the most easily corrected complications.

After recovery from the attack every effort should be made to prevent recurrence by increasing the general resistance of the patient and by adequate treatment of any debilitating disorder, particularly those just mentioned. Relief from overwork, administration of tonic drugs and especially removal to a cooler climate are to be recommended. Particular efforts should be made to retain the resistance and the nutrition of the patient at a high level during the spring and early summer of the following year because of the danger of recurrence at this time. Public charity may do much to better the resistance of poverty-stricken pellagrins, but it sometimes happens that the particular handicap of the patient cannot thus be relieved, and this is especially true of those pellagrins who are already in comfortable financial circumstances. Such patients may require a careful study of their general condition and a careful regulation of their lives for a period of several years.

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THE ABSENCE OF PANCREATIC SECRETIONS IN SPRUE AND THE EMPLOYMENT OF PANCREATIC EXTRACT IN THE TREATMENT OF THIS DISEASE.

By Thomas R. Brown, M.D.

BALTIMORE, MD.

Our ideas of sprue as a clinical entity date from the works of Manson, Vander Burg and Fayrer in the '80s, although it has been recognized since 1737, and Hillary clearly defined it in 1766. Manson described it as a disease of the tropics, characterized by "a peculiarly inflamed, superficially ulcerated, exceedingly sensitive

condition of the tongue and mouth; great wasting and anemia; pale, copious and often loose, frequent and frothy, fermenting stools; very generally by more or less diarrhea, and also by a marked tendency to relapse." Castellani and Chalmers, in the last edition of their *Manual of Tropical Medicine*, 1919, define it as follows: "Sprue is a chronic catarrhal inflammation of the alimentary canal of unknown cause, characterized by a peculiar ulcerative condition of the tongue and mouth and by the passage of large, pale, smooth motions, the symptoms waxing and waning periodically." The disease is endemic in certain parts of Asia, affecting primarily the Europeans, though the natives are not immune, and it is widely distributed all through the tropics (under various names, such as Ceylon sore-mouth, psilosis, diarrhea alba, aphthæ tropicæ, etc.), while ever increasing communication between tropical and temperate countries has resulted in more and more cases being seen in Europe and in North America. Recently renewed interest has been aroused in the United States of America in the subject of sprue by the work of Wood, who calls attention to the fact that a certain number of cases regarded as atypical pellagra, and seen in our Southern States, are in reality mild but definite cases of sprue. Unquestionably, living in hot, humid climates, previous wasting diseases and improper diet render one more susceptible to the disease, but the definite etiologic factor or factors have not as yet been absolutely determined, although, at the present writing many authorities, probably the majority, are in favor of regarding the disease as due to a monilium infection. Kohlbrugge's theory that the disease is due to infection by Monilium or Oïdium albicans has been supported by Bahr and others, though Castellani has described several other varieties of monilium in the stools of patients with sprue, while Ashford believes that it is not Monilium albicans but another parasite—Monilium psilosis—that is the cause of the infection, and he and others believe that they have definitely proved this by immunologic and vaccine studies, by agglutination and complement-fixation tests and by feeding experiments on monkeys with reproduction of the disease. Dold and others, however, believe that "an excessive acid- and gas-producing microbe is an essential factor in the disease," and "that in various countries different kinds of organisms having the same pathologic effects will be found causing this disturbance." In this connection it may be mentioned that Castellani has reported a number of cases markedly improved by the administration of large doses of bicarbonate of soda, while certain writers believe that the disease is produced by certain cocci or protozoa. Unquestionably the two theories most supported are either that the disease is in reality a moniliasis, due to one or several varieties of this fungus or that it is due to dietetic errors and probably represents a real deficiency disease, as McCarrison has especially suggested.

As one would expect from the symptoms, most authorities lay special stress upon the *pathologic anatomy* of the disease as it affects the *digestive tract*, although Manson has insisted that while certain of the findings undoubtedly represent the *primary* lesions due to the disease, others unquestionably represent the effect of the *secondary* long-lasting tissue starvation due to the disease and are very similar in character to the intestinal findings in famine patients. Certainly in all severe, chronic cases there is "an irreparable destruction of the mucous membrane of the alimentary canal both of the secreting and absorbing tissues" (Manson), all leading to the thinned intestine with diaphanous wall, with absence or marked diminution of villi and glands, congestion, ulceration and erosion, and sometimes cicatricial replacement, which are obviously basic causes of the digestive symptoms which dominate the picture and which are due to the effect of such a pathologic condition upon the digestion and assimilation. Microscopically we meet with small-cell infiltration, a smooth and atrophic mucous membrane, small follicular ulcers, notably in the lower ileum, the primary lesions, according to Castellani, being beneath the epithelium in both the tongue and intestine, the former producing the peculiar mouth picture so characteristic of the disease.

Certainly, whatever the primary causes, digestion and absorption are very markedly affected by the pathologic conditions produced, and the acids produced in such abundance must markedly disturb digestion, notably the emulsification and digestion of the fats, so that there is often 40 to 50 per cent. of undigested fat in the stools. Certain authorities believe also that the changes that have been described in the liver leading finally to atrophy lessen so markedly the detoxifying properties of this organ as to add a definite picture of intestinal toxemia to the other symptoms of the disease.

Strange to say, after a very careful searching of the literature we have been unable to find in detail any careful notes as to the microscopic changes in the *pancreas* in sprue; most authors, such as Manson and Schmidt, do not mention it at all in their description of the pathology of the disease; others content themselves with stating that the pancreas is normal, inflamed or cirrhotic, this probably based on macroscopic findings, as no note is made of the microscopic examination of this organ.

In 1916 we published[1] the results of our quantitative studies of the pancreatic ferments in a case of sprue sent to us from Porto Rico, and finding that all three ferments—trypsin, lipase and diastase—were absent, administered pancreatin to the patient in addition, of course, to the recognized treatment of this disease, and were very much struck with the remarkable improvement that took place, an improvement coincident with the administration of

[1] Johns Hopkins Hosp. Bull., October, 1916, No. 308.

pancreatic extract and stopping with a recurrence of the symptoms shortly after the pancreatic extract was withdrawn, so that for the patient to remain perfectly well clinically it was essential to administer the extract constantly. While many had suggested that there was a diminution or absence of pancreatic ferments, as obviously suggested by the character of the stools, notably the large excess of undigested fat therein, we believe that ours was the first case in which this was definitely proved by very careful and repeated estimations of these ferments.

Since our first case we have had the opportunity of studying 4 other cases—thus making 5 in all—2 coming to us from Porto Rico and 3 from the Philippines. All had been diagnosed as sprue by experts in this disease and were of long duration, and in none had the symptoms been present for less than one year. In each case the symptoms were typical: gradual onset, sore-mouth, diarrhea very marked in the morning, indigestion, increasing loss of weight, diminished appetite in 4 of the cases, abdominal discomfort, much gas, a marked tendency to ballooning of the abdomen, which in one of the cases was of the maximum degree, often coming on with no apparent cause and producing great discomfort; the tendency to relapse had been noted in each of the cases. The stools were characteristically frequent, voluminous, frothy, gray in 4 cases, yellow in one, with mucus, many bacteria, acid reaction and marked excess of fat; we did not, however, make very careful studies of the stools for monilium or other intestinal parasites. By proper methods bile pigments could be demonstrated in the stool in every case, and the gray color, therefore, was not due to lack of bile but was probably caused by leukourobilin—a not at all improbable transformation in the absence of pancreatic secretions—although Castellani believes that in certain cases this color is due to various bacteria, as, for instance, Bacillus albafaciens.

Our *quantitative* estimation of the pancreatic ferments was made from studies of the stool in all our cases and from the duodenal contents obtained with the Einhorn bucket in 3 cases. These quantitative estimations of the ferments in the stool were made once in 1 case, twice in 3 cases and five times in 1 case, there being an interval of nearly a year between the third and fourth and fourth and fifth estimations. The methods employed were those previously described by us;[2] for the diastase we used a modification of the Wohlgemuth method, for the trypsin the Fuld casein method, for the lipase 1 per cent. monobutyrin, while the same methods, with slight modifications in regard to dilution, were used in estimating the ferments in the duodenal contents. In both our 5 cases, both in the original experiments and in the repetitions of the tests, whether with the stool, which we regard as more exact quantitatively, or

[2] Johns Hopkins Hosp. Bull., September, 1912, No. 259; July, 1914, No. 281 and elsewhere.

with the duodenal contents, none of the pancreatic ferments was found, or in such minimal amounts as to fall within the limits of error. Thus in the case of diastase we had previously estimated the low normal amount of this ferment in the stool after the method which we had described and which was based on the study of a large number of normal cases.[3] This low normal amount we found to be 600 starch gram units, but in each of our cases of sprue the reading showed less than 12 units, this being our tube of greatest dilution, as we regard it as impossible to draw any conclusions as to lesser amounts than this. All these findings are so striking that we feel that it is beyond question that certain of the chronic cases of sprue are associated with a complete absence of pancreatic secretion, and this must play a role in the production of the symptoms, although, of course, our series is far too small to deduce from it any general conclusions. We should have liked to have estimated quantitatively the intestinal ferments in these cases as well, but the inherent difficulties are so great and the readings obtained so open to criticism that this procedure was not carried out. Nevertheless, if one can judge from the pathologic findings there must be an enormous diminution in the intestinal ferments, and the effect of the absence or diminution of certain of these, such as erepsin, enterokinase, the inverting ferments, possibly the duodenal hormone which brings about pancreatic secretion, and, at the same time, the disturbances in the chemistry of the chyme, notably as regards reaction and character of the bile, must play an enormous role, not only *per se*, but in the effect of these variations from the normal upon the secretion of the pancreatic juice. Whether this absence represents organic changes in the gland, whether it is due to functional disturbance or to destruction or changes due to lack of activation of the ferments after they have reached the duodenum, are obviously questions which we are unable to answer. In regard to the gastric contents of our 5 cases, 1 showed hyperacidity, 2 subacidity, 2 achlorhydria, but in the case of these last two groups a return to a practically normal gastric contents was coincident with the very marked clinical improvement noted; the one case that showed no improvement under treatment was that associated with hyperchlorhydria. Both the cases with achlorhydria showed a return of acid very shortly after they began to show improvement in symptoms. Castellani has noted that the test-meal may show diminished hydrochloric acid and pepsin, while Van der Scheer found no special changes in either gastric secretion or gastric motility in his 13 cases. Certainly, in our small experience the gastric picture is neither constant nor significant.

In regard to *treatment*, the usual therapeutic measures in vogue—encouragement, absolute rest, fresh air, sunshine and a very carefully selected diet—were used in all cases. As regards diet, in the 4 of

[3] Johns Hopkins Hosp. Bull., July, 1914, No. 281.

our cases that did so well a diet beginning with buttermilk, which we chose in place of ordinary milk because these cases showed deficiency of acid in the gastric juice, then gradually adding egg, zwieback, bread-and-milk and other simple, soft and liquid foods, including fruit juice and purée of fruits, was so well borne that there was no need of trying other special diets. All these cases had obviously tried change of climate but none had been given monilia vaccines. In the fifth case—the one that showed no improvement whatsoever on this diet— we tried fruit diet and meat diet, with special attention to strawberries in the former, but neither was well borne; in fact, all diets seemed to be equally poorly borne, and the only means of helping him seemed to be courses of neosalvarsan intravenously, and this produced a marked temporary improvement, as it had done previously in his case in the Philippines. In the cases with subacidity or anacidity we gave hydrochloric acid until their gastric contents gave practically normal figures. In the case with excessive hydrochloric acid we used sodium bicarbonate in large amount, but, if anything, this seemed to add to his distention and his discomfort. We did not try yellow santonin, so strongly recommended by Begg, nor did we think appendicostomy and irrigation, as suggested by Van der Scheer, advisable or justifiable.

In all of our cases, based on our finding of the complete absence of pancreatic secretion, we gave large doses of pancreatin or some form of pancreatic extract, 5 to 10 grains, with 20 to 40 grains of calcium carbonate or calcium lactate three times daily, two hours after the larger feedings; in 4 of the cases the results were really so remarkable, the treatment seemed so markedly efficacious and the improvement so rapid as to make each one feel that it was definitely due to their being supplied with the ferments in which they were deficient. This improvement persisted as long as the treatment continued; 3 of the 4 cases were lost sight of in three or four months after the treatment started, but they seemed clinically much better. The fourth case—a patient who had moved from Porto Rico to Virginia and was constantly near enough to be seen every few months—continued well so long as she took the pancreatin; in fact, while on the treatment she was clinically absolutely free of all signs and symptoms of the disease and looked and seemed absolutely well. On the other hand, if she stops the pancreatin for a few days the tongue becomes sensitive and sometimes red, she developed a morning diarrhea and the abdomen feels distended and uncomfortable, and the stool becomes more voluminous and unquestionably shows increasing fermentation. But all these symptoms rapidly disappear with the readministration of the ferment. This case has been carefully studied a number of times in the years that she has been under our observation, but the stool still always shows a complete absence of secretion from the pancreas, and it is quite obvious that, in her case at least, health is absolutely dependent upon the regular and

constant administration of pancreatin. The fifth case showed absolutely no benefit from the use of pancreatin; his was the longest history—over three years—although on admission he apparently was by no means so ill as our first case—the one who has been studied the most carefully of our series, though he was definitely more ill clinically than the other three. We have felt in his case that the destruction of glandular tissue was so great that there must have been such reduction in intestinal ferments, in addition to his complete pancreatic insufficiency, that he was unable to either digest or assimilate more than the very minimum amount of food, and, in this case, we should have liked to have tried intestinal ferments and possibly liver extract in addition to what we were giving—whether they would have produced any benefit is obviously problematical.

These cases are far too few in number to justify us in drawing definite general conclusions in regard to the pancreatic secretions in sprue, but we do feel that they add something to our knowledge of the secretory disturbances met with in this disease and are worth recording, both from the point of view of pathology and of treatment. The careful study of these cases leads one to certain queries anent this disease: Is sprue one or several diseases? Are the major portion of the symptoms due to the primary lesion or are many of them much better explained on the basis of secondary starvation? Is it possible to explain the picture on the assumption that it represents an infection due to a monilium and, if so, is one or several species involved? Or may various organisms or groups of organisms having the common quality of producing marked acid fermentative changes in the chyme bring about these symptoms? What role does diet play? May this possibly be a new member of the ever-increasing group of deficiency diseases? Is sprue very much more widely disseminated in temperate climates than has hitherto been supposed and may it play some role in certain of the vague chronic digestive disturbances so frequently met with in countries which lie in the southern portions of our temperate zones, for example, our southern states.

Whatever our answer be to these queries, we do feel that the study of our cases shows that in certain at least of the chronic cases of the disease (1) there is a practically complete absence of the pancreatic ferments, and (2) that while, obviously, all the well-recognized forms of treatment—dietetic, hygienic, etc.—should be rigorously carried out, nevertheless very great improvement and, in some cases, apparently clinical cure can be brought about by regular and constant administration of pancreatin.

EPINEPHRIN HYPERSENSITIVENESS AND ITS RELATION TO HYPERTHRYROIDISM.*

By Francis W. Peabody, Cyrus C. Sturgis, Edna M. Tompkins
and
Joseph T. Wearn,
Boston, Mass.

(From the Medical Service of the Peter Bent Brigham Hospital.)

There are at the present time two procedures in extensive use in this country for the determination of functional hyperactivity of the thyroid gland. One of these, the measurement of the basal metabolism, rests on sound experimental and clinical observations, for there is abundant evidence that stimulation of the thyroid gland or administration of its active principle induces an increase in heat production. There can be little doubt that stimulation of metabolism is an important feature in hyperthyroidism and that the measurement of the metabolism is a valuable index of the degree of activity of the thyroid gland; but we are still in the dark as to how far other associated features combine with this and go to make up the clinical symptomatology of hyperthyroidism. The outstanding drawback to this method for the determination of thyroid activity is that even with the recently simplified technical procedures it requires specialized training and experience both for its application and for the proper interpretation of the information derived from it.

The second procedure consists of the injection of epinephrin and its diagnostic significance depends on the type of reaction which has been described as occurring in patients with hyperthyroidism, and which is supposed to be characteristic of this condition. The test is usually carried out by the method suggested by Goetsch, and 0.5 c.c. of a 1 to 1000 solution of epinephrin is administered.†

* Read before the meeting of the Association of American Physicians, Atlantic City, N. J., May 5, 1920.

† The tests were actually carried out in the following manner, as described by Wearn and Sturgis (Arch. Int. Med., 1919, xxiv, 247): "The patients remain at absolute rest in bed for a period of one hour. If there is restlessness or apprehension they should be reassured and every effort made to obtain mental as well as physical quiet. At the end of the rest period control readings of the blood-pressure, pulse- and respiratory-rates are made at five-minute intervals. Also at this time a note is made as to the presence of nervousness, precordial pain, dizziness, palpitation or any other symptoms which may be significant. Likewise the objective condition of the patient is observed, and it is recorded if any of the following signs are present: tremor of the hands, sweating, coldness of the hands, throbbing of the neck, epigastrium or over the precordium and pallor or flushing. At the end of an hour's rest in bed the patient is usually quiet and has few complaints; the blood-pressure and heart-rate are normal or there may be a slight tachycardia (in sharp contrast to the patient with exophthalmic goiter in whom a more marked tachycardia persists even when at rest in bed). Likewise after the rest period there is little to record from an objective or subjective standpoint. If this condition

The "positive" reaction which has been assumed to indicate hyperthyroidism consists of the production of a rise of systolic blood-pressure of at least 10 mm. of mercury or a rise in pulse-rate of at least 10 beats per minute, together with an increase of such signs and symptoms as tremor, sweating, vascular pulsation, nervousness and palpitation. The test is so easy to apply and apparently so simple to interpret that it has been widely adopted as a diagnostic measure, and the "positive" reaction is frequently considered as an indication even for surgical interference. On account of this tendency to regard the test as highly specific in its significance, it has seemed to be of importance to study in more detail the nature of the reaction to epinephrin and to determine the conditions under which the "positive" reaction, which may be assumed to indicate epinephrin hypersensitiveness, appears. Such studies have been carried on at U. S. Army General Hospital No. 9, Lakewood, N. J., and at the Peter Bent Brigham Hospital, Boston. The present communication is a brief summary of the results.

As far as is known the difference between "positive" and "negative" reactions to epinephrin is a quantitative one, and what clinical significance the test possesses depends on the selection of a proper differentiating dose. Even so small an amount as that used (0.5 c.c. of a 1 to 1000 solution) probably produces some effect in everyone. In subjects reacting wholly "negatively" it has been found that the basal metabolism is temporarily raised from 5 to 15 per cent., while in those reacting "positively" the increase is from 15 to 30 per cent.[2] No such effect is observed, even in nervous subjects, from the prick of a needle or from the injection of salt solution. Under given circumstances the effect of the drug seems to remain fairly constant in a given individual.

A fundamental part of the investigation obviously consists of

approaching the normal has not been attained then the control readings should continue further, for with nervousness, tremor, sweating, tachycardia or possibly other prominent signs already present it would be difficult to judge the effect of the epinephrin. In a few patients the control readings of blood-pressure and pulse remained at a level slightly above the normal, but the injection of epinephrin was carried out after they became constant. In a number of patients venepuncture was done at the end of the rest period for blood-sugar determinations, but when this or any other disturbing factor is introduced it is necessary that subsequent control readings be made, and these should agree with the preliminary readings before the test can proceed. After satisfactory control readings have been made, 0.5 c.c. of a 1 to 1000 solution of epinephrin, freshly prepared, is injected deep into the deltoid muscle. In all of these tests the solution was made by adding one $\frac{1}{30}$ grain of Parke, Davis & Co. adrenalin brand of epinephrin tablet to 1 c.c. of water, thereby making a 1 to 1000 solution. After the injection four or five readings are made of the blood-pressure, pulse- and respiratory-rates at two or three-minute intervals, and also at these times any change in the objective or subjective condition of the patient is noted. After the first few observations readings are continued at five-minute intervals until one hour after the injection, when ten-minute readings are made for a period of one-half hour, thus making the observation period one and a half hours from the time of the injection. From our experience at Lakewood it would seem that the time of observation could safely be cut to one hour, as we have failed to observe anything of importance after that length of time."

the "control" observations carried out on normal individuals. These were begun in the army, and it was soon found that the problem was complicated by the fact that our standards of normality were not clearly defined. A number of patients in the hospital for minor surgical ailments turned out to be hypersensitive to epinephrin. Analysis of their past histories and of their characters suggested that while they were normal men, judged by the usual standards, they were not the types from which good soldiers are made. From the point of view of the army the "normal control" must be the soldier who can withstand the strain of hard training. A group of 26 men from an organization which had undergone training for fourteen months and was on its way overseas were therefore studied and none of these were found to give "positive" reactions to epinephrin. These were, of course, selected normals, for they were men of unusual physical endurance and nervous stability. A second group of normal men tested consisted of 28 Harvard medical students, and among these 4, or 14 per cent., gave perfectly definite "positive" reactions. Four other men showed transient rises of pulse-rate of over ten beats per minute, or of a systolic blood-pressure of more than 10 mm., or both. But as these were usually noticed only on one observation and not accompanied by the characteristic symptoms they were not regarded as giving "positive" reactions. In many other "negative" cases slight increase in blood-pressure and pulse-rate were noted. In addition to this there is a third group which may also be properly considered among the normals. These were patients at General Hospital No. 9 on whom the diagnosis of "effort syndrome" was made—men who, for the most part, would pass in civil life as within the bounds of normality but who developed symptoms, usually of a psychoneurotic nature, under the nervous and physical strain of army life. The exact nature of this condition is still uncertain, but there is very general agreement that hyperthyroidism plays no part in it. The clinical picture is not similar to that of hyperthyroidsim; the subjects improve under therapeutic measures that make patients with hyperthyroidism worse, and the basal metabolism is normal. If so common a condition as "effort syndrome" represented even a mild or incipient type of hyperthyroidism it is almost inconceivable that definite cases should have been so rare in the army. Among 143 cases of "effort syndrome," 69, or 48 per cent., reacted "positively" to the epinephrin test. These results are not unlike those obtained by Boas,[3] who reports that 28 per cent. of 21 cases of "effort syndrome" gave "positive" reactions. In association with this type of subject one may also consider the observations made on a small number of definite psychoneurotics—individuals who cannot be classed as wholly normal because the symptoms arising in the course of a normal life induced them to seek medical advice, but persons, on the other hand, in whom no evidence of organic disease,

either of the thyroid gland or of any other organ, could be found. Among 7 such subjects all were found to give "positive" reactions to epinephrin.

Summarizing the observations made on the various groups of subjects without evidence of organic disease, one finds that hyper-

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	HANDS	MISCELLANEOUS
9.00	–	–	–	–	COLD	RESTING QUIETLY
9.05	–	–	–	–	"	" "
9.09	–	–	–	–	"	" "
9.15	EPINEPHRIN 0.5 CC. 1:1000 SOLUTION INTRAMUSCULARLY					
9.18	V. SL.	–	–	–	COLD	RESTING QUIETLY
9.21	–	–	–	–	"	" "
9.24	–	–	–	–	"	" "
9.27	–	–	–	–	"	" "
9.30	–	–	–	–	"	" "
9.35	–	–	–	–	"	" "
9.40	–	–	–	–	"	" "
9.45	–	–	–	–	"	" "
9.50	–	–	–	–	"	" "
9.55	–	–	–	–	"	" "
10.00	–	–	–	–	"	" "
10.05	V. SL.	–	–	–	"	" "
10.10	+	–	–	–	"	" "
10.15	+	–	–	–	"	" "
10.20	+	–	–	–	"	" "
10.25	+	–	–	–	"	" "
10.30	+	–	–	–	"	" "

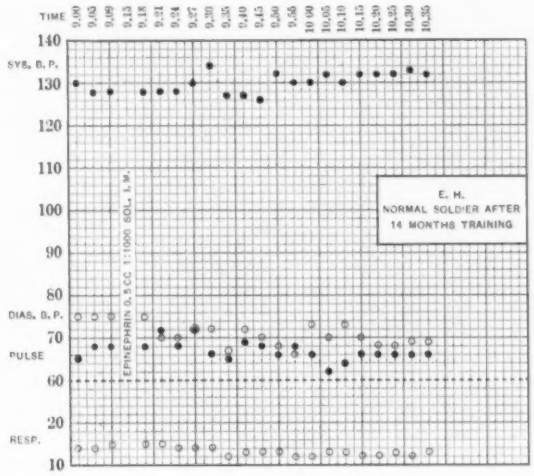

CHART I

sensitiveness to epinephrin is certainly not characteristic of the hardened soldier, that it occurs in about 14 per cent. of average young men, such as medical students, that it is present in nearly 50 per cent. of the type of young men who broke down under military training with the picture of "effort syndrome" and that it is still more common among definite psychoneurotics. It is difficult not

to see some relation between epinephrin hypersensitiveness and what one may call a "nervous constitution." On account of what is generally accepted as being known about the physiologic action of epinephrin, one is tempted to regard the test as indicating a hypersensitiveness of the sympathetic nervous system. It is frequently possible to select, on the basis of clinical study, the subjects who

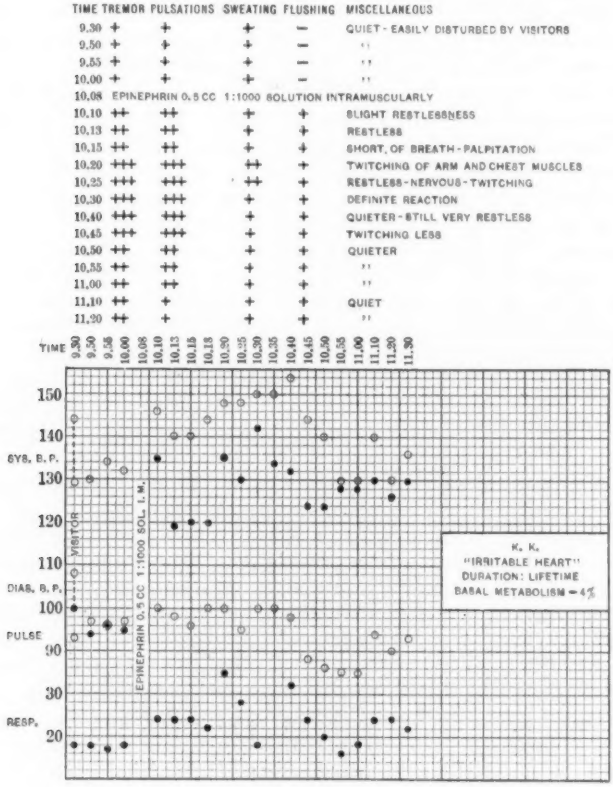
TIME TREMOR PULSATIONS SWEATING FLUSHING MISCELLANEOUS
9.30 + + + − QUIET - EASILY DISTURBED BY VISITORS
9.50 + + + − "
9.55 + + + − "
10.00 + + + − "
10.08 EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY
10.10 ++ ++ + + SLIGHT RESTLESSNESS
10.13 ++ ++ + + RESTLESS
10.15 ++ ++ + + SHORT OF BREATH - PALPITATION
10.20 +++ +++ ++ + TWITCHING OF ARM AND CHEST MUSCLES
10.25 +++ +++ ++ + RESTLESS - NERVOUS - TWITCHING
10.30 +++ +++ + + DEFINITE REACTION
10.40 +++ +++ + + QUIETER - STILL VERY RESTLESS
10.45 +++ +++ + + TWITCHING LESS
10.50 ++ ++ + + QUIETER
10.55 ++ ++ + + "
11.00 ++ ++ + + "
11.10 ++ + + + QUIET
11.20 ++ + + + "
TIME
SYS. B. P.
DIAS. B. P.
PULSE
RESP.
VISITOR
EPINEPHRIN 0.5 CC 1:1000 SOL. I. M.
K. K.
"IRRITABLE HEART"
DURATION: LIFETIME
BASAL METABOLISM = 4%

CHART II

will react to epinephrin, but this is by no means always the case. Even after considerable experience with the test one is liable to fall into error. There are many highly "nervous" or "neurotic" people who do not react "positively," and there are occasional persons who have no apparent neurotic tendencies who react violently to the drug.

The epinephrin test has also been used on various other types of

hospital case. Among 17 patients with organic heart disease, 3, or 17 per cent., gave "positive" reactions. This corresponds closely with the 14 per cent. of "positive" reactions found in the group of medical students, and it is possible that the figure represents approximately the average incidence of the reaction among normal persons. Incidental observations have also been made on cases of syphilis, chorea, asthma, acromegaly, epilepsy, diabetes, dementia precox and hyperthyroidism, and one or more "positive" results have been obtained in each condition. In a series of 21 patients who were convalescent from acute infections, 12, or 57 per cent., gave "positive" reactions—a figure in close agreement with results obtained by F. M. Smith,[4] who found that 50 per cent. of 50 cases following influenzal pnemonia reacted "positively." Nicholson and Goetsch[5] report 19 "positive" reactions among 40 cases of questionable or definite tuberculosis, a percentage incidence of 47. One case observed at General Hospital No. 9 seems particularly worth noting. A boy with an organic heart lesion, but otherwise normal, gave a "negative" test. A few days later he had an attack of acute tonsillitis which was followed by a tonsillectomy. A repetition of the test, after convalescence from the operation, gave a "positive" result. This evidence certainly suggests that infections may induce a hypersensitiveness of the sympathetic nervous system, and there are, of course, various clinical symptoms which are in harmony with such a conception. To assume, however, that there is necessarily an associated hyperacidity of the thyroid gland seems quite unwarranted, if only for the reason that many of these post-infectious cases improve with graduated exercises, a type of treatment wholly unsuited to patients with hyperthyroidism. It is true that in certain cases with hyperthyroidism the condition has apparently manifested itself after some acute infectious disease, but the reverse is still more striking, for the development of outspoken hyperthyroidism after acute infections is without question more rare than it would be if there were stimulation of the gland in nearly one-half of the cases of acute infectious disease.

Case.	Disease.	Positive.	Negative.	Doubtful.
2	Pneumonia	2	0	0
3	Diphtheria	2	1	0
9	Acute rheumatic fever . . .	4	4	1
1	Acute tonsillitis (tonsillectomy)	1	0	0
6	Scattered	3	3	0

Special attention has been paid to the epinephrin test in hyperthyroidism. The diagnosis in the cases reported on was based on the classic signs and symptoms and the history, together with the determination of the basal metabolism. Twenty-one cases have been studied, and in 15, or 71 per cent., "positive" reactions were obtained; 6 unquestionable cases, 4 in early stages and 2 in later stages, with basal metabolism ranging between 21 and 35 per cent.

above normal, gave "negative" epinephrin reactions. No relation was noted between the intensity of the reaction to epinephrin and the apparent severity of the case. One patient, with a basal metabolism 61 per cent. above normal, was considered to be extremely toxic but gave a comparatively slight reaction, while a mild case, with a basal metabolism 26 per cent. above normal, gave a very severe reaction. Nine patients were tested on whom thyroidec-

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	HANDS	MISCELLANEOUS
10.15	++	++	++	+	COOL	ONLY FAIRLY QUIET-MOVES ARMS AND HEAD
10.25	++	++	++	+	"	" " " FEW MOVES
10.35	++	++	++	+	"	" " " " " "
10.40	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY					
10.41	+++	++	++	PALE	COOL	NO CHANGE
10.44	++	++	++	PALLOR GONE	"	" "
10.48	++	++	++	+	"	" "
10.57	++	++	++	+	"	THINKS HER HEART IS BEATING FASTER
11.02	++	++	++	+	"	NOTICES NOTHING ELSE
11.07	++	++	++	+	"	FAIRLY QUIET
11.14	++	++	++	+	"	" "
11.22	++	++	++	+	"	" "
11.28	++	++	++	+	"	" "
11.38	++	++	++	+	"	" " NO SIGN OF REACTION
11.44	++	++	++	+	"	" "
11.52	++	++	++	+	"	" "
12.02	++	++	++	+	"	" "
12.08	++	++	++	+	"	" "

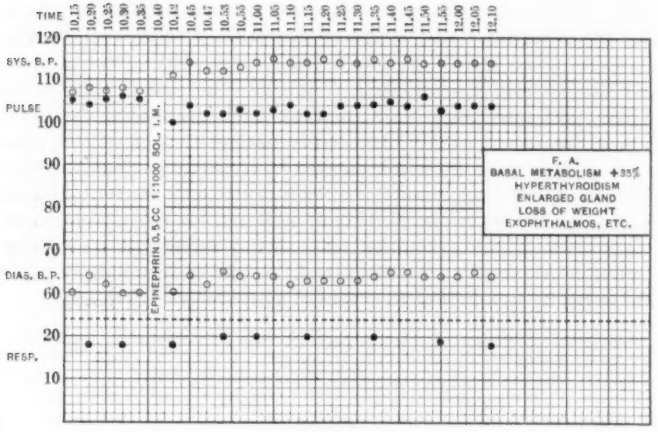

CHART III.

tomies had been done two or three years previously and who had been living normal lives without symptoms for a year or more. Five of them gave "negative" reactions, while 4, in whom the basal metabolism was −18 per cent., −15 per cent., −1 per cent. and +12 per cent., gave "positive" reactions.

The general conclusions which it seems justifiable to draw from our observations are as follows:

1. Different individuals, both sick and well, react with different degrees of intensity to the injection of epinephrin. By means of selected dosage of the drug and carefully chosen criteria for the response, one can differentiate, somewhat artificially, between the slight reactions which are called "negative" and the more violent

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	MISCELLANEOUS
3.15	++	++	+	++	VERY RESTLESS - MOVING CONSTANTLY
3.20	++	++	+	++	" " " "
3.22	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY				
3.25	++	+	+	SL. PALLOR	RESTLESS AND MOVING
3.30	++	+	++	++	RESTLESSNESS INCREASING
3.32	+++	++	+++	+++	NERVOUS, EXCITED, THROBBING
3.35	+++	+++	+++	+++	NERVOUSNESS INCREASING, APPREHENSIVE
3.40	+++	++++	+++	+++	MARKED REACTION
3.45	+++	+++	+++	+++	SOMEWHAT QUIETER
3.50	+++	+++	+++	+++	" "
4.00	+++	+++	+++	+++	" "
4.05	+++	++	++	++	NERVOUSNESS DECREASING
4.15	++	++	++	++	" "
4.25	+++	++	++	++	" "
4.45	+++	+	++	++	" "
4.55	+++	+	++	++	STILL MORE RESTLESS THAN AT START

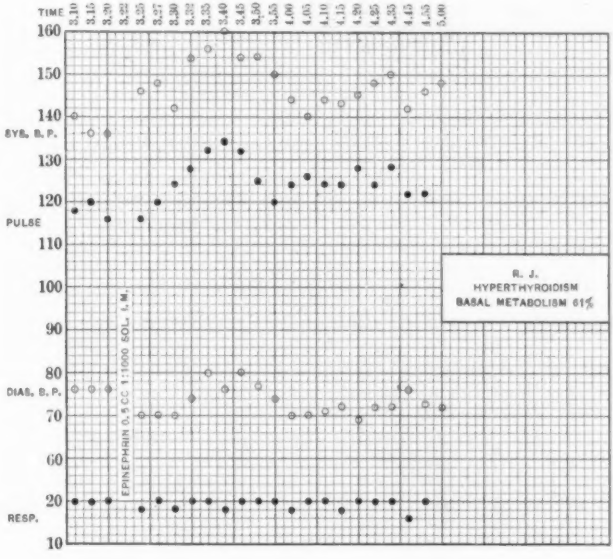

CHART IV

reactions which are called "positive." In certain instances "doubtful" or "questionable" reactions are obtained.

2. The fundamental nature of the reaction is unknown. It is associated with a rise in heat production which runs more or less parallel to the intensity of the reaction. On the basis of what is definitely understood with regard to the physiologic action of

epinephrin it seems probable that the phenomenon is due to a stimulation of the sympathetic nervous system. Theoretically a

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	HANDS	MISCELLANEOUS
9.50	+	+	−	+	WARM	QUIET
9.55	+	+	−	+	"	"
10.03	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY					
10.05	++	++	−	+	WARM	QUIET
10.07	+++	+++	+SL.	SL. PALLOR	COOL	RESTLESS AND NERVOUS
10.10	+++	+++	+	+	"	MORE RESTLESS AND GENERALLY NERVOUS
10.15	+++	+++	+	+	"	REACTION INCREASING
10.20	++++	++++	+	+	"	" "
10.25	++++	++++	++	+	WARMER	GENERALLY UNCOMFORTABLE
10.30	++++	++++	++	+	"	
10.35	++++	++++	++	+	"	REACTION NOW MARKED PALPITATION, RESTLESSNESS, VERY NERVOUS, FEELS QUEER
10.40	++++	++++	++	+	"	NUMEROUS EXTRA SYSTOLES
10.45	++++	++++	++	+	"	REACTION CONTINUES
10.50	++++	++++	++	+	"	" "
10.55	++++	++++	++	+	"	
11.00	++++	++++	++	+	WARM	
11.05	++++	++++	++	+	"	BEGINNING TO FEEL BETTER QUIETER
11.15	++++	++++	+	+	"	HEART ACTION REGULAR FEELS "FINE"
11.25	++++	++++	+	+	"	
11.35	++++	++++	+	+	"	NOW FEELS COMFORTABLE

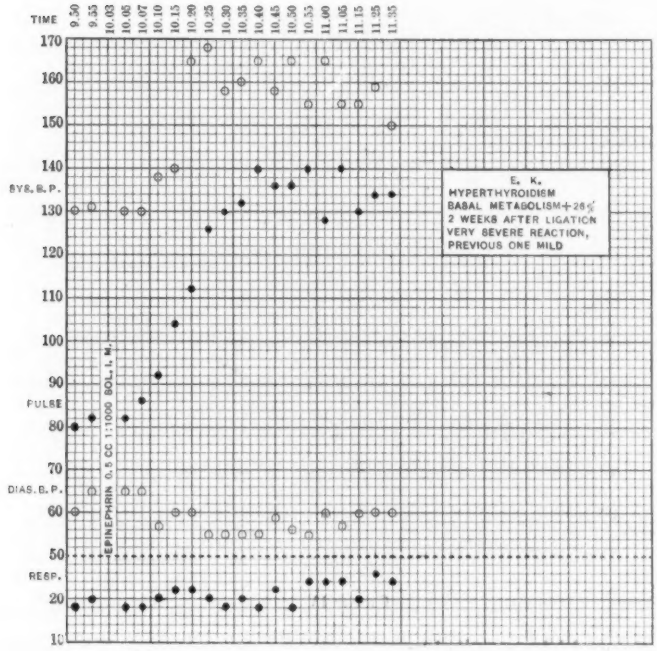

CHART V

"positive" reaction might indicate hyperactivity of the thyroid gland, of the adrenal glands or of the sympathetic nervous system. It might, on the other hand, depend on a lowered threshold of

response of the sympathetic nervous system. With the exception of hyperthyroidism little is known about these conditions in man, but they probably occur and there would seem to be no reason for assuming that a "positive" epinephrin reaction is constantly associated with hyperthyroidism. It is much more likely that different causes account for the reaction in different types of clinical cases.

3. Hypersensitiveness to epinephrin is found in many patients with the clinical picture of hyperthyroidism and with an increased basal metabolism, but it is not constant under these conditions.

4. Hypersensitiveness to epinephrin is also found in persons who have no indications of hyperthyroidism. Thus it was present in many psychoneurotics in about 50 per cent. of patients convalescent from acute infections, in nearly the same proportion of soldiers with "effort syndrome," in 14 per cent. of apparently normal young men and in patients with various unrelated diseases.

5. The "positive" reaction to epinephrin appears to occur most often in highly nervous individuals, but it is not constant in such persons. The clinical significance of the reaction is not clear, but at present it should certainly not be regarded as having any specific significance in the diagnosis of hyperthyroidism.

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THE USE OF DIET IN THE TREATMENT OF CHRONIC ARTHRITIS.

By Ralph Pemberton, M.D.,
VISITING PHYSICIAN TO THE PRESBYTERIAN HOSPITAL, PHILADELPHIA.

In a series of previous contributions the writer has published the results of laboratory and clinical studies upon chronic arthritis which reached their fullest development in the course of observations upon soldiers in the army.[1] The scale upon which these last observations were conducted was much larger than has heretofore been possible in this country under controlled conditions, and in addition to yielding side lights upon existing views, afforded further data and directed attention along new lines.

[1] Pemberton, Buckman, Foster, Robertson, Tompkins: Studies on Arthritis in the Army Based on Four Hundred Cases, Arch. Int. Med., March, 1920, xxv, 231–282; April, 1920, xxv, 335–404.

One of the chief methods of investigation employed arose from earlier observations upon the relation of a limited food intake to the incidence and perpetuation of the symptoms of chronic arthritis. In the course of this investigation, clinical experience in the application of dietary control to this disease was not a little amplified, and the matter was further placed upon a firmer foundation by a number of laboratory findings.

The writer's personal acquaintance with colleagues at scattered points, as well as correspondence and indirect information from others not personally known to him, has indicated that these methods are being utilized in the treatment of arthritis, and it seems important to direct attention to several considerations. The purpose of this article is therefore to make brief mention of the added experience gained in the application of diet to arthritis; to call attention to the greater justification for the use of these methods which laboratory observations have afforded; to point out the place which these methods occupy in relation to other forms of therapy in this disease; and, finally, to direct attention to the limitations in the application of these methods, to the precautions which must be observed and to the possible dangers from neglect of these precautions.

Without going into details which have been elsewhere fully published (*loc. cit.*) mention can here profitably be made, by way of preface, to several of the positive findings in the army studies above referred to. There were observed a very slight lag in the eliminations of salt and water in arthritics as compared to normals; a basal metabolism slightly lowered in 20 per cent. of the cases; a high blood creatin which tended to disappear as cases improved; a lowered sugar tolerance which was found to accompany arthritis more or less in proportion to its severity. Essentially normal data were obtained regarding the blood fats and cholesterol, the blood calcium and the blood urea and non-protein nitrogen. The statistical findings regarding etiology, distribution of involvement, etc., need not be referred to here.

The lowered sugar tolerance was determined by the administration of 100 grams of glucose by mouth and the subsequent estimation of the percentage concentration of glucose in the circulating blood. In 200 observations on 60 arthritics this lowered sugar tolerance was found to grow less or disappear as convalescence proceeded, whatever the method of therapy, but it returned to normal most abruptly after the removal of causative foci of infection. A lowered sugar tolerance is not specific for arthritis and should be interpreted only as reflecting part of the underlying pathology of this disease which, on a number of counts that cannot here be detailed, apparently consists in an interference with the respiratory functions of the circulating blood. These do not, however, express them-

selves conspicuously in terms of the end-metabolism as shown by basal metabolism studies.

As already mentioned the application of the principle of a reduced diet to arthritis received amplification in the above studies, particularly as to its use in combination with other forms of treatment and as to the vigor with which it could be applied. An attempt will therefore be made to outline the manner in which the dietetic handling of a case can be most simply carried out and then to indicate the limitations and contra-indications to this therapy.

A preponderating number of chronic arthritics, if placed upon a sharply reduced intake of food or on a starvation basis, will show within a period of one to four days a betterment in their subjective feelings, lessened tension of the soft tissue, and an added freedom of movement. The improvement may follow upon intercurrent surgical operations of many kinds and examples of such improvement, together with criteria as to the early evidences of clinical betterment, are detailed in the references already given. The improvement under sharp dietary restrictions may and generally will be seen, even in the presence of causative foci of infection, because the principle under which it acts is that of catering to a weakened function, probably an oxidative function, dislocated in most cases by some inflammatory process usually in the form of focal infection. Following upon a chronic focus of infection, however, there may be a more or less permanent dislocation of normal physiology, as illustrated by the lowered sugar tolerance, such that removal of the focus is not sufficient to restore it, and it is particularly for this reason that disappointing results so frequently follow the removal of definite infectious foci. Notwithstanding the possibility, however, of demonstrating the benefits from a reduced caloric intake even in the presence of focal infection, therapy based upon this should never be attempted in the presence of such removable infection. This is one of the precautions which the writer desires to emphasize in the strongest possible manner. It would be obviously unsound to attempt treatment by adjusting conditions to the limitations of a weakened function if the cause of that weakened function can be removed. There are contra-indications to the removal of foci which make such action justifiable occasionally but the chief field of use for dietetic therapy in active arthritis is that in which focal infection definitely cannot be demonstrated, or, better, has been definitely removed without further clinical improvement.

In cases of chronic arthritis suitable for dietetic therapy, treatment must be carried at least to the point where the individual is spared the necessity of metabolizing as much food as he had been previously ingesting. There are unfortunately few criteria, except subsequent clinical improvement, of the degree to which the diet must be reduced, and it therefore follows that it is generally useful

to know what the accustomed caloric intake of a given case has been under the average conditions of his invalidism. This is by no means always essential, but it becomes so more or less in proportion to the severity of a case and the prospective difficulty of treating it. If the patient be ingesting customarily a fairly large amount of food, say 3200 calories, it is obvious that this quota can be significantly reduced to, say, 2200 calories without great detriment to his nutritive needs, at the same time sparing him about 1000 calories. If, on the other hand, the accustomed food intake of an arthritic be 2000 calories or less, as is frequently the case in later stages of the disease, the administration of a diet of 2300 calories would not only fail to achieve its purpose but might tend to aggravate existing conditions. The writer has therefore found it useful to determine over a period of a week or ten days, under conditions approximating the average life of an individual the accustomed food intake in terms of calories. This can be done within a relatively small margin of error in any modern hospital where the services of a trained dietitian are available. It is also useful occasionally, in chronic cases, to know the percentage distribution of calories from protein, fat and carbohydrate, because of the indications that of all these foods carbohydrate is the chief offender by virtue of its quick combustion and the large role which it plays in average dietaries. Such an estimation, however, is not essential and the total calories are of greater importance. It has been determined over a considerable series of arthritics that relatively early cases of arthritis in good nutrition, accustomed to a food intake of 2800 to 3000 calories or more, may do very well from the start and shortly recover entirely following a reduction of their caloric intake to about 2000 calories. It is often possible in these cases to increase this total by two or three hundred calories, preferably from fat, a few weeks after convalescence is well established. Under these circumstances dietetic therapy, by catering to a mildly weakened function, has one of its happiest results. In more extreme types problems of much difficulty may arise, although the principle of treatment is not altered. If, for example, as above mentioned, the accustomed daily caloric quota has been for a year or more 1800 or 1900 calories, any attempt to spare the metabolic functions by cutting this down may be at the further expense of nutrition as a whole and can be carried out only with the greatest caution. The experience of the profession with diabetes has shown the degree to which low diets can be often successfully borne, but in view of the fact that arthritis is not a fatal disease *per se* the justification for applying them to it must be very clear.

When it becomes necessary to institute a food intake below 1800 calories it is well to begin at the highest level from which, *a priori*, any results can be expected, say 1500 calories. If results are not forthcoming at this level it may be necessary to reduce the total for a short time to 1200 or 1300 calories, in anticipation of

which an intermediary period of "feeding-up' may be advantageous. At about 1500 calories the arthritic confined to a wheeled chair or to bed may easily maintain a fair nutritive balance but below that point conditions of undernutrition are established and should not be entered upon without considerable familiarity with this field and the possible dangers entailed. Short periods of undernutrition at these levels are, of course, not necessarily fraught with danger, but unless constituting part of a specific program are likely to do more harm than good. The early clinical betterment which is inaugurated, but cannot necessarily be maintained, leads to false encouragement and unnecessary depletion. The general nutrition of a subject is an important factor in determining the degree to which treatment can be pushed and the individual, not the arthritis, must often determine the vigor of treatment. It is of small benefit to improve the arthritis at the serious expense of the patient's health as a whole.

In addition to treatment by a reduced dietary, however, it is sometimes possible by an absolute fast to demonstrate quite dramatically a marked change in nearly all the manifestations of a severe arthritis. The adoption of such procedures, however, is not to be recommended for general use at the present time because of the critical undernutrition which results and because of the very disturbing if not dangerous complications which may arise. In the studies in the army, previously mentioned, is given a detailed account of a case treated along these lines with most gratifying end-results in so far as the active arthritic process was concerned (Case 22 of the above report). The soldier in question was again under observation almost a year later and was found to have maintained his freedom from active arthritis and to have gained greatly in strength and activity. It is, nevertheless, partly to direct attention to the untoward results which may follow such measures if carelessly applied and to urge the greatest caution in conducting them that the present article is contributed.

In addition to the precautions urged above must be mentioned again the limiting influence, in a given case, of such factors as anemia, undernutrition, intercurrent diseases of various kinds, functional nervousness and greatly lowered morale from invalidism. Coöperation, persistence and courage on the part of the patient are almost invariably required, and even in the most promising cases the physician may have to supply the *vis a tergo* in respect to each of these.

It is the misfortune of clinical medicine that the recognition of a new method of therapy is almost invariably followed by some unwise and extreme application of it. There is no such thing as a panacea or specific in our armamentarium, and, as a rule, injuries from abuse are necessary before wise utilization of any new therapy is possible. The present writer cannot hope entirely to escape this

result but can at least urge conservation and caution until the possibilities for good and evil have been more thoroughly worked out. This is of the greatest importance because the benefit to be derived in a definite percentage of arthritics from the method under discussion is now quite beyond dispute.

As a result of the studies above mentioned, and also of work now under way, the nature of arthritis can now apparently be definitely categoried, and indeed pretty clearly outlined.

Over a year ago the writer gave the reasons for his belief[2] that arthritis is due to interference with the processes of oxidation, possibly in the respiratory functions of the blood, and some outline of the manner in which this operates is given in a recent summary of some known and suggested facts related to arthritis, together with a hypothesis as to its nature.[3]

Space will not permit of discussing this question further at this point, but suffice it that the principle of action seems to apply to cases of all severity except that, in the more severe types, "catering" to a weakened function in the manner described may not alone suffice to restore altered physiology to normal. The situation is perhaps analogous to that presenting in cardiac decompensation, where the keynote of all treatment is rest. After a certain degree of decompensation is established, however, rest alone is not adequate and must be reinforced by such therapy as digitalis although the guiding principle must still be maintained.

By the same token, advanced arthritis should be treated with a clear understanding of the basis upon which therapy should be built, and one of the results arising from increased experience with this disease lies in appreciation of the fact that combinations of different kinds of treatment will often achieve results where dependence upon one measure alone will fail. Thus if the arthritic be spared unnecessary metabolic burdens he will often respond more readily to such a measure as hydrotherapy which by itself is too frequently unavailing. From the evidence now at our command it seems more than probable that reduced diet, hydrotherapy, the iodides, arsenic and certain other agents really act all in the same direction, differing chiefly in the manner in which they accomplish their end-result. Caution must again be urged here, however, against the depletion which may follow several coincident lines of attack unless critically carried out.

From what has been said it is obvious that no rule can be advanced for determining the level of the appropriate diet in any given case, but the nearest approach to such a help is based upon the recognized approximate requirement of 30 calories per kgm. of body weight under resting conditions. If reasonable precautions be observed this is probably a safe nutritive level under most circumstances, and

[2] Address before the New York Academy of Medecine, November 16, 1919.
[3] Jour. Am. Med. Assn., December 25, 1920, No. 26, vol. lxxv, p. 1759.

if the total calories so determined be contrasted with the caloric level under the previous conditions of the individual's life the observer will often be surprised at the sharp reduction evidenced. It must not be supposed, however, that this will necessarily achieve the desired result in all cases. It is probably fair to say, however, that this level should be established in many refractory cases as a foundation for other forms of therapy that might otherwise be inoperative.

The details of the composition of diets constructed along the above lines have been already fully published and space will not permit of their repetition here.[4] Attention should be called, however, to the principle of giving the individual as much satisfaction as possible at his meals by serving bulky substances of small nutritive worth. It is thus possible to provide what appears to be a fairly generous meal, although the amount of actually nutritious substances, such as eggs, bread, butter, milk, etc., which form the source of the calories in the diet may be very limited.

It may be useful at this point by way of illustration to cite two instances of improvement through the combination of several measures on the basis of a restricted diet.

Miss B., aged twenty-seven years, had for several years suffered from a violent widespread arthritis of the proliferative type characterized by atrophy of the joint structures and great swelling of the soft tissue surrounding them, most evidenced in the hands. She had been through nearly every conceivable form of examination and treatment, including removal, on principle, of her tonsils, but without benefit. The only thing which had proved of any value was thyroid extract and this induced such a serious disturbance on its own account that it was discontinued. She then relapsed. The accustomed food intake of this patient under uninfluenced conditions average about 2415 calories. She was then placed upon a caloric level of 1558 calories for three weeks, with definite evidences of improvement, in the form of relaxation in the soft tissues of the phalanges of the hands and subjective *bien aise*. After several changes of diet following a gastro-intestinal upset it became clear that the above caloric intake should be further reduced, as conditions were apparently stationary. She was therefore placed upon 1358 calories to which was added a very cautious regimen of sweats every other day, and in a few days experienced distinct further benefit. It is hoped later to publish further details of this case together with certain laboratory observations.

Another instance of benefit following the application of orthodox measures after the removal of an unnecessary "metabolic load" is the following already published in the studies quoted.

[4] Am. Jour. Med. Sc., May 1917, No. 5, vol. cliii, p. 678. The Metabolism and Treatment of Rheumatoid Arthritis. Fourth paper. Ralph Pemberton, M.D.

Stg. Hays, aged twenty-nine years, had suffered for two years from a progressive and ankylosing arthritis chiefly of hands and wrists. Two months after tonsillectomy and several months after removal of dental foci there was no improvement. A careful search could reveal no other focus of infection. Observation of this patient for eleven days showed him to be ingesting an average of 3000 calories per diem. He was then placed on a diet of 2051 calories and twelve days later there was unquestionably less tenderness and swelling, and probably greater freedom of movement than at any time during the two months of observation. This improvement was maintained for some weeks, when his condition became stationary after about 50 per cent. improvement. After some oscillations of diet he was again placed on the same regimen, to which were added hydrotherapy cautiously conducted, potassium iodide and cod-liver oil. Further improvement was again inaugurated, and about a month later he left the hospital, with no evidence of active arthritis anywhere.

Attention should be directed to the fact that in the early stages following the institution of a sharply reduced diet there may be a rapid loss of weight. Under these circumstances improvement of the arthritis may be very striking, due to the fact that catabolism is running ahead of anabolism. This condition can be compared to the hastened metabolism following such stimuli as radium and the roentgen ray. As the plane of basal metabolism falls, however, to a lower level and becomes adjusted there with equilibrium of weight, improvement may be much less obvious or may even cease entirely. At this time there may indeed be in severe cases or in those in which the appropriate level of diet has not yet been reached, an exacerbation at some point notwithstanding the recent improvement.

It is at this time the test of the applicability of a diet arrives and it then becomes necessary either to hasten metabolism further by means of several agents available to this end, hydrotherapy, arsenic or possibly potassium iodide, or else further to reduce the diet in the manner discussed. The principle of betterment under a reduced diet may be well illustrated under these circumstances, and yet the clinical application of it may fail unless these relations be appreciated.

In a few cases under the writer's care no beneficial influence from a reduced diet could be detected, much less carried to a clinical conclusion. The proportion of cases, however, which show no evidence of favorable operation of the principle of a reduced diet, even short of true clinical betterment, is small in the writer's experience; but there seem undoubtedly to be some such instances, and one should be prepared to meet them. It should also be remarked that even during improvement under properly adjusted dietary conditions there may be exacerbations at one or more points temporarily interrupting progress. If these be treated

symptomatically or even left alone and the main principle adhered to they will often subside, become less severe and frequent as time goes on and finally disappear.

Attention has been previously directed to the fact that when convalescence is thoroughly established an increased caloric intake is often possible sometimes to such a degree that the individual can resume his previous activities with even added efficiency.

It is impossible, without going to too great length, to particularize regarding factors and signs which should be observed in carrying a case of arthritis over the long road to recovery. Experience alone will yield them. The point has been reached, however, at which a further addition of exact data has placed the treatment of arthritis by low caloric feeding upon a basis more secure than existed previously, so that the principle of application can be appreciated even in the presence of departures from rule. It is hoped to publish further data in this connection in the not distant future.

THE PATHOLOGY OF BRONCHIAL ASTHMA.

By Nai Kamchorn, M.R.C.S., Eng., L.R.C.P., Lond.,
CHIEF OF THE MEDICAL DEPARTMENT,
AND
A. G. Ellis, M.Sc., M.D.,
PATHOLOGIST, SIRIRAJ HOSPITAL, BANGKOK, SIAM.

Twelve years ago one of us (A. G. E.) discussed in this Journal[1] the pathology of bronchial asthma as based on a study of 7 previously reported cases and 1 personally added. The conclusion reached at that time was that there is no constant or definite change in the bronchi of persons dying during an attack of this condition. Since that time 3 additional cases have been reported. The history of one of these was published in the *Transactions of the German Pathological Society* for 1909. The other 2 are the more recent ones of Brown[2] and Boughton.[3] The first 2 are not accessible to us.

The case of Boughton was reported as one of death from anaphylaxis and followed the injection of one minim of horse serum as a desensitizing agent. The effect of the injection of that minute quantity of serum was a typical attack of bronchial asthma, with fatal termination, in forty-five minutes. The subject was an otherwise healthy man who for ten to twelve years had suffered attacks of asthma when in proximity to horses. Post mortem the lungs

[1] 1908, cxxxvi, 407. [2] Asthma, St. Louis, 1917.
[3] Jour. Am. Med. Assn., 1919, lxxiii, 1912.

showed emphysema. Microscopically there was a little mucus and a few desquamated epithelial cells in some of the bronchioles—not more than a slight catarrhal bronchitis if it can be called that. Boughton does not mention the sputum of this patient.

To these cases we can now add a twelfth, recently studied in Siriraj Hospital. Clinically it is of interest because of the family history of asthma in four generations. Furthermore, the duration of the disease, with attacks from childhood to the age of fifty-two years, would supposedly lead to permanent histologic changes in the bronchi if such ever occur in this affection.

History of Case. The patient was a Siamese man, aged fifty-two years, at one time an actor but chiefly engaged as a fishmonger at a seaside town. He did not smoke opium nor Indian hemp. His grandmother (father's side), father, an uncle and an aunt had asthma and the patient's third child is also suffering from the affection.

Patient since childhood had suffered from attacks of asthma, which at first were at long intervals but gradually became more frequent. Three months before admission to the hospital his feet and legs began to swell, this finally including the whole body. Coughing and shortness of breath were for a long time prominent symptoms, both gradually becoming more marked. On admission the man was edematous, ascitic, cyanosed and had respiratory dyspnea, with abdominal breathing and respirations, thirty-four to the minute. He had a troublesome cough, productive of white, tough sputum (this was not examined in the laboratory). Rales were present, especially over the bases. The precordial area was resonant and heart sounds weak. Treatment gave no relief; the patient gradually became worse and died on the eleventh day after admission, clinically from heart failure.

Postmortem Findings. The body was edematous. All the serous cavities, except the left pleura, which was obliterated by adhesions, contained a marked quantity of serum. The right auricle and ventricle were dilated and contained fluid blood under pressure. The wall of the right ventricle was 1 cm. thick. The left ventricle was moderately dilated; the muscle was red and firm. Valves and vessels were normal.

The left lung was collapsed to about one-half the usual size. The incised surfaces were dark bluish-red in color. Crepitation was much lessened but there was no actual consolidation. The bronchial mucosæ were intensely red. In the middle-sized and smaller bronchi was tenacious mucus, but not in great quantity.

The lower lobe of the right lung was like the left and the bronchi were similar. The upper and middle lobes were overdistended and at the apex were subpleural blebs. These lobes pitted on pressure, were pale and on incision dripped frothy serum. Crepitation was

lessened but there was no consolidation. The bronchial mucosa in these lobes was pale and the luminæ contained no exudate.

The abdominal organs contained an excess of blood. Summary: Hypertrophy and dilatation of right ventricle; dilatation of right auricle and left ventricle; bilateral chronic adhesive pleuritis; partial atelectasis of left lung and lower lobe of right; vesicular and interstitial emphysema of upper and middle lobes of right lung; acute bronchitis of left lung and lower lobe of right; congestion of spleen, kidneys, stomach and liver; anasarca; multiple serous effusions.

Spreads of the exudate in the bronchi are of leukocytes and many columnar epithelial cells. In the cellular mass is much mucus and a number of very typical Curschmann's spirals. Charcot-Leyden crystals are not present and staining reveals only an occasional eosinophile.

Microscopically the partly collapsed portions of the lungs contain considerable black pigment, with at points fibrous tissue increase around it. Most of the epithelial lining of the bronchioles is desquamated and its place is occupied by leukocytes, nearly all mononuclear, which also partly fill the lumina. The vessels in the walls are intensely hyperemic and the tissues are densely infiltrated by mononuclear cells. In the middle-sized bronchi epithelial desquamation varies in degree, but in general is less than in the smaller ones. In the lumina are many mononuclear leukocytes and some red blood cells. In some of these larger tubes is a small quantity of mucus but no spirals. In none of the bronchi are crystals or eosinophiles. There is no evidence of fibrous tissue thickening of the bronchial walls nor does the muscularis mucosa appear abnormal. The larger bloodvessels are somewhat sclerotic. The bronchi in the expanded portions of the right lung have much less marked changes, indicating that the compression atelectasis of the other parts had increased the catarrhal changes.

The histology of the bronchi may therefore be summarized as that of an acute catarrhal bronchitis. We have in this case then to deal with a man who had had increasingly frequent attacks of asthma since childhood, but with no greater changes in the walls of his bronchi than might develop in a few days during an acute inflammation without asthma. As to the bronchial content, spirals are, of course, not commonly found in catarrhal exudates, but they have been encountered, according to Kaufmann, in cases of lobar and bronchopneumonia, fibrinous bronchitis, pulmonary edema and behind bronchial stenosis due either to enlarged pigmented glands or peribronchial malignant tumors. They are therefore not specific either in origin or in significance when found in the sputum, although, of course, much more common in cases of bronchial asthma. Nothing in the structure of the bronchi explain their formation in any case.

In conclusion, these additional cases still further emphasize the conclusions of the former paper, namely, that the histology of the bronchi does not explain the course of bronchial asthma. The length of time a person suffers from the disease and the number of attacks he has are apparently without effect upon the bronchi. The theory of spasm of the bronchial muscles, while not thus proved, is by each case increasingly favored.

INFLUENZA.*

By Channing Frothingham, M.D.,
Boston, Mass.

In considering the subject of "influenza," it is important to have clearly in mind to just what disease one is referring. The disease which will be discussed in this communication is the one which appeared as a pandemic in the autumn of 1918 throughout the United States and has appeared subsequently, with pretty general distribution, during the winters of 1918–19 and 1919–20. Just what relation this disease, which appeared in pandemic form, bears to the conditions ordinarily spoken of as influenza, grippe, fever of unknown cause, acute respiratory infection, etc., is not clear. It is possible that the pandemic disease was simply one of these in which the virus had become temporarily intensified, but it seems more likely that it was an independent disease.

In order to have a clear conception of this condition called influenza, it is exceedingly important to separate the disease itself from the subsequent complications. This is rendered additionally difficult because the etiology of the pandemic disease is not settled. If the influenza bacillus eventually turns out to be the cause of this pandemic disease, many of the lesions which are now looked upon as complications will have to be considered as part of the disease.

The etiology of this pandemic disease has been the subject of considerable discussion. This has narrowed itself down practically to the question of whether the influenza bacillus described by Pfeiffer following the epidemic in 1889–90 or some other unknown organism was the causative agent. At one time it was suggested that this pandemic disease might be some form of the plague, but it is now felt by most authorities that such was not the case. Folley[1] aroused considerable interest in regard to the etiology of this disease by reporting the presence of a coccobacillus similar to the plague organism in the blood serum in many of these cases, but his findings have not been confirmed by other observers.

* Presented at the meeting of the Alumni Association of the Medical Department of the University of Buffalo, June 10, 1920.

In favor of the view that the influenza bacillus was the cause of the pandemic disease is the frequency with which it has been recovered from the secretions of the nose and throat. Opie[2] and others and Roos,[3] among others, have shown that this organism was present frequently in the secretions from this part of the body. Wolbach[4] in his autopsy studies found the sinuses leading off from the upper respiratory tract frequently infected and in many cases recovered a pure culture of the influenza bacillus. Roos by injecting the influenza bacillus produced lesions in the bronchial tract and also a leukopenia in rabbits. It is a well-established fact that during the early stages of this pandemic disease the leukocytes in the blood stream were usually diminished. Huntoon and Hannum[5] have isolated an endotoxin from cultures of the influenza bacillus which has produced a specific lesion in the lungs of mice. They also found no serologic characteristics which would interfere with the claim that the influenza bacillus was the etiologic factor in this pandemic disease. Ferry and Houghton[6] found congestion throughout the various organs of guinea-pigs and marked prostration in rabbits following injection with the influenza bacillus, both of which symptoms occurred in man during this disease. Blake and Cecil[7] have produced in monkeys by inoculation with the influenza bacillus a disease which they consider similar to the pandemic disease in the human.

Against the opinion that the influenza bacillus was the etiologic factor in the cause of this pandemic disease may also be arrayed a considerable amount of experimental evidence. In many instances the influenza bacillus has not been isolated from the upper respiratory tract even after careful bacteriologic studies and also the influenza bacillus has not been recovered in the blood cultures by various observers including Matz.[8] Rosenau and Keegan,[9] as well as Goldberger and Lake,[10] endeavored to produce this disease in human subjects by various experimental procedures with the influenza bacillus, and in all cases were unable to do so. Bloomfield[11] has placed different strains of the influenza bacillus upon normal mucous membranes of the upper respiratory tract but has not produced any disease by this experimental procedure. Valentine and Cooper[12] feel that this pandemic must have been produced by one specific organism, and consider the fact that various strains of the influenza bacillus were found among the different cultures is an argument against the pandemic having been due to the influenza bacillus. Tunnicliffe[13] found that the opsonic curve toward the influenza bacillus was not influenced during the course of this disease and therefore considers that this organism is not the etiologic factor. Goodpasture and Burnett[14] have reported the presence of lesions in the lungs which they consider typical of the cause of this pandemic disease in certain cases in which the cultures from these lungs have remained sterile. As the influenza bacillus was frequently recovered from the lungs in

their cases its absence in these cases with typical lesions makes them feel that it was simply one of the secondary invading organisms. Neal[15] brings out the fact that during the pandemic there was no more influenzal meningitis than one normally meets, and he feels that one would expect a large increase in this type of meningitis if the disease were due to the influenza bacillus.

At the present time it is justifiable for difference of opinion to exist in regard to the etiology of this pandemic disease. For convincing evidence has not been presented either for or against the influenza bacillus as the etiologic factor. Park[16] states that the organism which produced this disease is as yet unknown and that the influenza bacillus was a frequent secondary invader. It certainly is fair to say that no other organism has been reported which may be considered as the producer of this disease.

In what manner this pandemic disease was spread is not established. It was assumed that direct extension from one individual to another by means of droplets from the respiratory tract containing the virus which contaminated the air, eating utensils, clothing, etc., was the method of transmission. Experimental work by Rosenau and Keegan[9] and Goldberger and Lake[10] have thrown considerable doubt upon this method of transmission because both sets of experimenters working independently were unable to infect human volunteers with secretions from the upper respiratory tract of patients ill with the disease. Leake[17] has continued experimental work with human volunteers along the same lines as these other investigators, and although he has failed in the great majority of cases to produce this disease by introducing human secretions from the respiratory tract of acutely ill patients into the upper respiratory tract of volunteers, he has in rare instances produced a disease similar to the one met with in the pandemic. The very rapid spread of this disease in a community was similar to that seen in water or milk-borne epidemics rather than the epidemics dependent upon direct extension from one person to another. Lynch and Cumming[18] have shown from a study of statistics that the washing of eating utensils by means which do not sterilize them and the wash water was a serious factor in the spread of this disease. Winslow and Rogers[19] feel that it was spread by human contact or the contamination of food, etc., because in Connecticut it was possible to keep certain communities free from the disease by strict quarantine.

In considering the pathology of this pandemic disease it is exceedingly important to keep separate the lesions produced by the disease itself from those dependent upon the secondary invading organisms. The respiratory tract presented the most striking lesions. Throughout the upper respiratory tract and bronchi the mucous membrane was markedly congested and hemorrhage into it was not infrequent. In the smaller bronchioles and the adjoining alveoli there was a degeneration and necrosis of the cells forming the walls resulting

in a peculiar hyalin formation. This has been reported independently by MacCallum,[20] Wolbach[4] and Goodpasture and Burnett.[14] At first there was very little fibrin deposited, but this sometimes appeared later. Into the air spaces from the injured walls hemorrhage often occurred. It is possible that this lesion progressed at times into a bronchopneumonia without any secondary invading organisms, but probably not. The bronchioles became dilated, probably due to the necrosis of their walls. This in some cases led to permanent bronchiectasis, but it also is not certain that this occurred unless some complicating organism was present. Actual ulceration of the bronchi has been reported by Lucke, Wight and Kime.[21] Escape of air into the interlobular tissue of the lungs with extension into the mediastinum and subcutaneous tissues sometimes occurred. Congestion of and hemorrhage into the bronchial lymph nodes was found. Hemorrhagic lesions in the adrenal gland similar to those found in other acute infections has been reported, and atrophy of the cells of the adrenals has been noted by Cowie and Beavan.[22] Degeneration of the parenchymal cells of the testes with little cellular reaction was noted by Wolbach.[4] Several observers have mentioned a hyalin degeneration of the recti muscles and acute arteritis has been noted in these and other muscles.

Although the lesions dependent upon the pandemic disease itself were somewhat limited except for the respiratory tract, the lesions resulting from the invasion by complicating organisms were most varied. Unfortunately many authors in describing the pathology of so-called influenza include the lesions produced by secondary invading organisms, which results in some confusion. The character of the lesions met with in the complications varied with the invading organism and the location of the lesion. The organisms which have been reported as complicating the pandemic disease are the influenza bacillus; all four types of the pneumococcus; the Streptococcus hemolyticus, the Streptococcus viridans; Staphylococcus aureus; Micrococcus catarrhalis; and the Friedländer's bacillus. If the influenza bacillus eventually is found to be the cause of this disease the lesions produced by it, of course, will no longer be considered complications.

Of the various complications the lesions produced in the lungs have been the most interesting and have received the most attention. Of these pulmonary lesions bronchopneumonia occurred most frequently, and usually was extensively scattered throughout both lungs. The areas of infiltration were often confluent so that extensive consolidation resulted. The cut surface of these lungs presented a characteristic appearance which was peculiar in the large amount of exuding serum and blood. The influenza bacillus was frequently recovered at autopsy in pure culture from the lungs with this type of bronchopneumonia. Other organisms were also found and probably this type of pneumonia was produced by various

organisms on top of the initial lesions produced by the pandemic disease. Patches or considerable areas of lobar pneumonia were frequently found, due probably to some one of the pneumococci. Actual necrosis of the lung and abscess formation have been reported. The healing of these various lesions took place by resolution or organization of the exudate. Dilatation of the bronchi with areas of infiltration of the lung tissue about them were quite common and the escape of air into the interlobular tissue of the lungs occurred as a complication, but it was not settled under just what circumstances these complications occurred. All sorts of combinations of lesions occurred and several different organisms were recovered at autopsy from the different lobes of the lung in the same individual. Although a lesion in the smaller bronchi and in the alveolar wall was produced by the etiologic agent of the pandemic disease, the appearance of a pneumonia, whether broncho or lobar in type, usually signified invasion with some other organism.

In the pleural cavity various lesions were found which it was assumed were due to secondary invading organisms. Simple fibrinous pleurisy, serous effusions, seropurulent effusions and empyema, free or incapsulated, occurred. In some cases numerous small pockets of pus separated by organizing connecting tissue were encountered. Various organisms have been recovered from these different conditions. In some rare instances air ruptured from the interlobular connective tissue into one or both pleural cavities producing a pneumothorax. In the pericardial cavity serous effusions, fibrinous exudates and collections of pus have been reported. These were undoubtedly all due to various types of secondary invading organisms.

Empyema of the sinuses connected with the upper respiratory tract was frequently found as well as suppuration in the middle ear and mastoiditis. Infection of the parotid glands has been reported. The bacteriology of these complications has been quite varied. General peritonitis has been reported and abscesses in the subcutaneous and muscular tissues from both of which various types of bacteria have been recovered presumably secondary invaders. The hemorrhagic lesions produced in the muscles by the virus which produced the pandemic disease probably were a factor in the formation of the abscesses.

The period of incubation of the disease has been reported as one or two days by Keegan,[23] and as two days by Bloomfield and Harrop.[24] It seems pretty well established that the disease can develop as quickly as this, but whether it did in all cases is not so certain.

In considering the symptoms of this pandemic disease it is important to separate the symptoms which were due to the uncomplicated disease from those which were dependent upon the complications. The symptoms varied in their severity and in the number which

appeared in an individual case. The suddenness of the onset of the symptoms was striking. In many cases the transition from perfect health to marked prostration occupied only a few hours. The severity of the prostration was often marked. In addition to the prostration muscular pains throughout the body, headache, chills or chilly sensations, and nausea were usually present. Vomiting and diarrhea sometimes occurred. Usually coryza was met with at the start, but this and the appearance of the cough was delayed for one or two days in some cases. Cough, dry tickling throat, sore-throat and hoarseness were also common symptoms. The patients frequently complained of nose-bleed, and it was quite common for menstruation to appear prematurely.

Upon examination the patient usually showed reddened conjunctivæ and pharynx. Fever was usually present. There was sometimes pallor but more commonly cyanosis was present even before any evidence of involvement of the lungs appeared. In some cases an erythematous rash suggesting measles appeared, in others purpuric spots and petechial hemorrhages occur. Lucke, Wight and Kime[21] reported the appearance of papules and vesicles which contained a slightly turbid fluid. Signs suggestive of meningeal irritation were frequently seen, and Stangl[25] reported a considerable number of such cases in his group. The spleen was occasionally palpable. Except for these signs the physical examination was essentially negative.

The usual routine clinical pathologic tests were negative except for a white blood count below the normal. Matz[8] found an elevation of the blood urea whether or not a complicating nephritis was present. He also claimed that some degree of acidosis occurred because the carbon dioxide tension in the blood was found diminished.

In many cases after a few days the fever subsided and the symptoms gradually disappeared. In a considerable number of cases, however, after a drop in the temperature about the second or third day, it became elevated again. This second elevation of the temperature in most cases signified an extension of the process into the lung with a beginning bronchopneumonia. It has not been definitely established whether this secondary rise in temperature always signified an invasion with some complicating organism or whether it was due simply to the extension of the existing process. At this stage of the disease the cyanosis usually became somewhat more pronounced. Upon physical examination in some cases there was no change in the chest signs, but usually signs of infiltration into the lung tissue began to appear. These varied from slight dulness or a few rales at some point over the chest to evidences of definite consolidation. In many of the cases evidence of infiltration of the lung tissue on both sides was found. As the process in the lung was an extension from a diffusely scattered lesion in the bronchi it was natural that the signs were found in both lungs. If one will remember

that the initial lesion started in the bronchi and the air spaces immediately surrounding them, one will appreciate that the lesions might be quite far removed from the chest wall. Therefore it was not strange, as Christian[26] pointed out, that the infiltration of the lung might be quite extensive before signs appeared.

In the cases in which the signs simulated a lobar pneumonia it must be remembered that the pathology of the condition showed frequently a confluent bronchopneumonia which gave the clinical signs similar to a lobar pneumonia. In these cases it was quite common for the character of the lung signs to change frequently not only from day to day, but often from hour to hour, so that at one time upon examination of the chest the signs suggested pleural effusion, at another a definite lobar pneumonia and at still another a bronchopneumonia.

In the cases in which some type of pneumonia developed a fatal termination occurred within a few days or the pneumonia dragged along for some time before recovery or death took place. In certain cases after the toxemia of the pneumonia had apparently been overcome the patient continued to be cyanotic and the case went on to a fatal termination with the appearance of suffocation from mechanical obstruction in the bronchi, so that air could not reach the lungs in sufficient quantity to carry on proper oxygenation of the blood. In those cases which recovered, however, the temperature dropped suddenly by crisis, as is seen in an ordinary lobar pneumonia, or it gradually returned to normal, as is seen usually in bronchopneumonia. This probably depended upon which type of secondary invading organism was present and also upon the character of the lesions produced in the lung. During this stage of the disease the leukocyte count remained low or it became gradually elevated. Even in the cases in which the pneumococcus has invaded the lung as a secondary invader the leukocyte count sometimes remained below normal throughout the disease.

A peculiar complication occurred in a few of these pneumonic cases which was met more often in some localities than others, namely, the appearance of air in the subcutaneous tissues of the neck with subsequent extension. Preceding the appearance of the air in the subcutaneous tissues above the sternum and in the neck there was pain beneath the sternum. This was probably due to the forcing of the air through the connective tissue of the mediastinum. This pain usually disappeared upon the appearance of the crepitation in the subcutaneous tissues of the neck. From this point the air sometimes invaded the subcutaneous tissues over the whole surface of the body extending upon the face, down the arms and the legs. It would seem as though there must have been some valvular arrangement at the point along the respiratory tract at which the air escaped into the tissues for this air to have forced its way through the subcutaneous tissue rather to have passed out the bronchi and

trachea. It is interesting that it was exceedingly rare for the air to break through the pleural surface into the pleural cavity. This extension of air into the subcutaneous tissue was not in itself a dangerous complication, because recovery took place in some of these cases even after extensive distribution of the air subcutaneously. It was gradually absorbed from the tissues and disappeared.

Various other complications have been described. These complications were, as a rule, dependent upon the invasion of some secondary organism and usually presented the picture expected for the particular organism. No attempt will be made to go into these complications in detail, but simply an enumeration of the various complications which have been reported will be made as follows: ulcerative stomatitis, osteomyelitis, endocarditis, pericarditis, empyema, peritonitis, various types of pleurisy, icterus, tachycardia, thyroiditis, cerebral thrombosis, neuritis, subcutaneous abscesses, otitis media, infections of the accessory sinuses and orchitis. Chronic bronchiectasis with resulting invalidism has followed some of the pulmonary complications. Meninger[27] reports that all types of psychosis followed this pandemic disease, and Fell[28] calls attention to the need of a guarded prognosis because the outcome was often different from what was expected. Meninger[29] also studied cases of neurosyphilis in order to see what effect the epidemic had upon them, and found that early cases of neurosyphilis were unfavorably influenced by the disease, that the late cases were not affected and that in no cases was the condition improved by the disease. Fishburg[30] and Murphy[31] brought out the fact that cases with tuberculosis stood the epidemic disease well and that the tuberculosis did not flare up following it.

No specific treatment has been recommended for this disease called influenza in the early stages before involvement of the lung has taken place, except the use of vaccines. Even the use of vaccines has been applied chiefly to the treatment of complicating pneumonia and therefore will be discussed later. Emphasis has been placed upon the importance of rest in the early stages of the disease and some reports suggest that in those instances in which the patients were promptly put to bed upon the first appearance of the disease pulmonary complications were less liable to develop. Carefully controlled statistics, however, in this regard are not available and comparison between the results obtained in different localities are quite unreliable. In view of the tendency for invasion of the lungs with various bacteria attempts to kill off organisms in the mouth have been made. For this purpose a mouth wash and spray, including quinin, has been recommended in an attempt to kill the pneumococci present in the upper respiratory tract. In some places all streptococcus carriers have been isolated from other patients in order to prevent the spread of this secondary invader. Herrick[32] has suggested that the edema of the lungs might be

diminished by the use of digitalis and venesection. On the other hand Keaton and Cushman[33] consider that death in these cases was the result of shock, and they considered that bleeding added to the possibility of shock. Breen, Bolling and Casper[34] recommend the use of coagulants to check the hemorrhage from the injured pulmonary vessels into the alveolar spaces. Tunnicliffe[13] recommends the administration of horse serum in order to stimulate leukocytosis. Cowie and Beavan[35] tried out adrenalin on the ground that there was a marked adrenal insufficiency in these cases without beneficial results. Therefore for the prepneumonic stage of the disease, rest, supportive treatment, forcing of fluids and diligent cleansing of the mouth are about all that can be done.

For the pneumonic stage of the disease, irrespective of whether this was produced by the etiologic factor of the disease itself or was dependent upon the secondary invasion of some complicating organism, various forms of treatment have been suggested. It was impossible to decide in many cases whether the pneumonia was the result of some complicating organism or not. If the leukocyte count in the blood was elevated some complicating organism was probably present, but if it remained low this test did not help differentiate, because pneumonias due to various organisms occurred, with low white blood counts. Examination of the sputum was done, but if organisms were found it was only suggestive that they were responsible for the pulmonary lesions. If the No. 1 pneumococcus was present in the sputum from the lungs the antipneumococcus serum against this organism was used. If this organism was not present the use of serum from patients convalescent from so-called influenzal pneumonia was tried in some communities. McGuire and Redden[36] first presented the results of the use of serum from convalescent patients, and their figures were so favorable that considerable impetus was given to this form of treatment. Redden[37] has more recently published the results of the use of this serum from patients who have recovered from an influenzal pneumonia and compared its use with the results from other types of human serum. He found that in order to be most effective the serum should have been collected from several patients who have recovered from a pneumonia. Stoll[38] has also tried out a variety of serums, and feels that the only one which was of any value was the one from patients who had recovered from so-called influenzal pneumonia. It must be realized that it was not definitely established just what was the cause of the pneumonia in the patients from whom the serum was collected. Therefore the specificity of the serum in relation to the cause of the pneumonia in a given case was uncertain.

The figures from the reports of McGuire and Redden[36] in the work done at the Naval Hospital in Chelsea show less mortality than most of the other reports from this part of the country, but attention must be drawn to the fact that not only the mortality

from this disease and its pulmonary complications varies considerably in different localities but even in the same locality at different stages of the epidemic. Therefore too much reliance must not be placed upon the results obtained from one hospital, especially when these results were not carefully controlled. Lord,[39] working at the Massachusetts General Hospital, and Locke,[40] working at the Boston City Hospital, have reported a small series of carefully controlled cases in which the serum from convalescent human patients was used as a therapeutic agent without any favorable results. Great caution must be used in giving credit to any special agent for apparently miraculous cures in those cases of pneumonia associated with this disease, because cases desperately ill have been observed in which recovery has occurred without any specific treatment. The opinion of the medical profession at present is considerably divided on the question of the therapeutic value of the serum from convalescent patients who have had influenzal pneumonia. It seems as though the enthusiasm for this form of treatment is diminishing. The author has never seen any benefit from the use of this serum, and is not in favor of its use.

Vaccines have been tried therapeutically for the various types of pneumonia associated with this disease, and also early in the course of the pandemic disease itself, with the idea of diminishing the number of cases of pneumonia. Koons[41] found the results satisfactory, but the use of vaccines was not sufficient or under enough control to form any opinion of their value. If a vaccine were used it was usually made up from several strains of the pneumococcus, one or more of the streptococcus and the influenza bacillus. The use of a typhoid vaccine intravenously was also tried without any striking results.

The injection of glucose intravenously in influenzal pneumonia has been recommended by Koons[41] and by Wells and Blaukinship.[42] They consider it was beneficial but without any specific reaction against the disease, and it must be given repeatedly. Until the value of some one of these so-called specific therapeutic agents has been more definitely established, one is justified in limiting the treatment of these complicating pneumonias to general supportive measures and the use of digitalis. The use of Type I antipneumococcus serum for those cases in which the complicating organism is the Type I pneumococcus is the exception.

The prognosis in this pandemic disease for the cases in which there were no complications or pneumonias was good. The incidence of pneumonia varied considerably in the different localities and with the stage of the epidemic. In the early stages of 1918 complicating pneumonias were reported in about 20 per cent, of the cases, and of these cases about 30 per cent. died, making a total mortality of about 6 per cent. for the disease, as practically all the fatalities were from pneumonia of some form. Subsequent flare-ups of the epidemic,

however, have not been accompanied with so much pneumonia nor has the mortality from the pneumonia been so high. In pregnant women the occurrence of pneumonia was reported at one time to be more frequent and the mortality figures given by Harris[43] were much higher than among other people.

Considerable interest has been aroused in regard to the possibility of vaccination as a prophylactic measure against this pandemic disease and as a prophylactic measure against the development of pneumonia as a complication of the disease. On the assumption that the disease was caused by the influenza bacillus, and as the pneumococcus and streptococcus were frequent secondary invading organisms in the lungs, vaccines were prepared by combining cultures of influenza bacillus with the various types of pneumococci and streptococci. Individual reports have been made by Rosenow and Sturdivant[44] and others favorable to the use of these vaccines not only in preventing the disease but also in diminishing the amount of pneumonia and the fatalities from it. Most of the work with vaccines has been carried out in regions in which the disease was already present, and therefore it was impossible to carefully control the experiments. McCoy[45] and his co-workers succeeded in studying the value of a protective vaccine under careful control and found that not only it did not prevent the disease but also it did not influence the incidence of pneumonia or the mortality from it. McCoy perhaps sums up the situation most clearly in his statement that figures from uncontrolled experiments seem to suggest that the vaccine is of value, but carefully controlled experiments show that it is of no use. On the assumption that this disease was spread by the dissemination of the virus by means of droplets from the respiratory tract, elaborate measures to prevent the spread of the virus by the wearing of masks, etc., have been suggested and tried out not only among the ill and their attendants, but among the entire population of a community. The value of such procedure in the absence of carefully controlled experiments is quite uncertain, and the sense of protection given to the public, if erroneous, may be harmful. Therefore some doubt exists as to the value of such procedures with our present knowledge.

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ACUTE NITROBENZOL POISONING WITH STUDIES ON THE BLOOD IN TWO CASES.*

By Robert F. Loeb, M.D., Arlie V. Bock, M.D.,

and

Reginald Fitz, M.D.,

Boston, Mass.

(From the Medical Clinic of the Massachusetts General Hospital, Boston.)

It is apparent that certain people in this country will drink various harmful substitutes for liquor as a result of national pro-

* This is study No. 13 of a series of studies on the physiology and pathology of the blood from the Harvard Medical School and allied hospitals.

hibition. Scott and Hanzlik[1] have already called attention to a group of individuals poisoned in Cleveland by alcohol denatured with nitrobenzol and have suggested that intoxication from this substance may be seen more frequently in the near future than in the past. An additional case in Philadelphia, reported by Donovan[2] and two others, which were recently seen in Boston at the Massachusetts General Hospital, bear out the suggestion of Scott and Hanzlik and make it seem of interest to review the pharmacologic action of this product and the clinical features of cases which have absorbed it.

Nitrobenzol, or oil of mibrane, is a coal-tar derivative resulting from the action of strong nitric acid on benzol and having the chemical formula of $C_6H_5NO_2$. It is a pale yellow liquid which smells and tastes like oil of bitter almonds. Its history in relation to internal medicine is interesting. It was discovered by Mitscherlich[3] in 1834, although it was not until 1859 that Caspar[4] introduced it to the medical profession as a new poison with toxic properties. The first fatal case described in England was reported by Letheby[5] in 1863. The first case described in America was reported by Stone[6] in 1904. Since 1859, however, so many single cases or groups of cases have been studied by various observers that our present knowledge of the effect of this poison upon the body is fairly comprehensive.

Nitrobenzol, according to Thompson,[7] is employed in the manufacture of high explosives and is used to a limited extent in perfumery, soap, confectionery and cookery processes in making dyes and in pharmaceutic laboratories. It is remarkable that a poison which is put to so many commercial uses should not be more toxic to people who handle it constantly. So long ago as 1863, however, Letheby remarked that "in every manufactory where nitrobenzole and anilin are prepared on a large scale the peculiar narcotic effects of these poisons are often observed. The vapors escaping into the atmosphere are breathed by the workmen and cause distressing headache and a heavy, sleepy sensation. For the most part these effects are not serious but are quickly relieved by fresh air and a mild stimulant, as a glass of brandy and water. Now and then, however, the workmen, from carelessness in their habits, expose themselves to the action of comparatively large quantities of these poisons, and then the effects are most dangerous."

In confirmation of this statement, Grandhomme[8] in 1883 reviewed all the published cases in nitrobenzol poisoning up to that date and

[1] Jour. Am. Med. Assn., 1920, lxxiv, 1000. [2] Ibid., 1647.
[3] Poisons: Their Effects and Detection, Charles Griffin Company, 1906, p. 193.
[4] Ibid.
[5] Pharmaceutical Journal, 1863, Series 2, v, 130.
[6] Jour. Am. Med. Assn., 1904, xliii, 977.
[7] The Occupational Diseases, D. Appleton & Co., 1914, p. 342.
[8] Die Thierfarben Fabriken, Koster, 1883, p. 17.

out of his series of 47 found only 4 which occurred in manufacture. Finally Miner[9] has recently pointed out that although almost all shoe dyes contain large percentages of nitrobenzol, yet shoe dye poisoning is rarely seen. It thus seems evident that the people who handle nitrobenzol as part of their daily work are not the ones who suffer the serious casualties from it most commonly.

Another interesting impression obtained from a survey of the literature of nitrobenzol-poisoning is that large numbers of cases have occurred more or less together at two different times. Grandhomme found that the majority of his cases occurred a comparatively short time after nitrobenzol was first used commercially. Since 1883, the time of his publication, but few new cases have been reported until 1919. Since that date, Stifel[10] has described 17 cases which were poisoned by nitrobenzol in shoe polish, Sanders[11] has added another case from the same cause, while Scott and Hanzlik, Donovan and the present paper have commented upon the group of cases which drank nitrobenzol as a substitute for liquor.

The pharmacologic action of nitrobenzol has been thoroughly studied. The most complete work upon the subject was reported by Filehne[12] at Erlangen in 1878. The most striking fact demonstrated by his experiments was that nitrobenzol kills by making the blood unable to transport oxygen. This occurred because the hemoglobin, in dogs at least, underwent a transformation from nitrobenzol into another form of hemoglobin having a characteristic spectroscopic absorption line which did not correspond to any of the ordinary hemoglobin products. Normal arterial blood if shaken outside the body with nitrobenzol did not show this change; on the other hand the blood of animals poisoned with nitrobenzol regained its power to take up oxygen after prolonged saturation with oxygen. Filehne's paper is of additional interest because of the deductions in regard to the treatment of nitrobenzol-poisoning drawn from his experiments. Aside from the obvious desirability of preventing this form of poisoning as much as possible, he suggested for the treatment of acute cases the transfusion of blood following copious bleeding.

The clinical appearance of cases poisoned with nitrobenzol is remarkably striking. One of the earliest English cases[13] is quoted in detail as affording a clear description of the condition as well as on account of its historical interest.

"A woman, aged thirty years, tasted a liquid which had been used for flavoring pastry, and perceiving that it was very acrid on her tongue and lips, spat it out immediately and washed her mouth with water. She thought she could not have swallowed more than

[9] Jour. Am. Med. Assn., 1919, lxxii, 593.
[10] Ibid., 395.
[11] Ibid., 1920, lxxiv, 1518.
[12] Arch. f. Exper. Path. u. Pharm., 1878, ix, 329.
[13] Quoted from Taylor: Guy's Hospital Reports, 1864, x, 193.

a drop, but in replacing the bottle she spilled about a tablespoonful on the table and did not immediately wipe it up. The vapor strongly impregnated the air of the small room in which she was, and produced a feeling of sickness in another servant. The burning taste in the mouth was immediately followed by a sensation of numbness and tingling in the tongue and lips and a strange feeling for the next hour. As the woman became worse, Mr. Fotherby was called in, and saw her in an hour and three-quarters after the occurrence. Her aspect was then quite typical of prussic-acid poisoning: The eyes were bright and glassy, the features pale and ghastly, the lips and nails purple as if stained by blackberries, the skin was clammy, and the pulse feeble. Her mind was then clear and she described how the accident occurred and what her sensations were. She was able to swallow a mustard emetic, after which she became rapidly worse, lost her consciousness, the teeth became set, the hands clenched and blue, the muscles rigid and convulsed. She vomited freely a pale fluid matter, which had the peculiar odor of nitrobenzol. The stomach-pump was used, but the fluid washed out of the organ had hardly any odor, owing, probably, to the small quantity actually swallowed and its removal by absorption. In about eleven hours there was reaction, consciousness returned and she was able to swallow. At the end of seventeen hours she was much better."

The striking points in this case and others are the slowness of onset of symptoms after exposure, the vagueness of symptoms until unconsciousness occurs but with gastro-intestinal symptoms and nervous symptoms being prominent, the characteristic color of the skin and mucous membranes and the rapidity with which return to normal occurs in patients who recover.

Letheby's pathologic report on his first fatal case gave an accurate account of the usual gross postmortem findings: "After death there were no appearances of convulsions but rather of narcotism and apoplexy. The face was flushed, the lips were livid; the superficial vessels of the body, especially about the throat and arms, were gorged with blood; the dependent parts were turbid; the blood was everywhere black and fluid; the lungs were somewhat congested; the cavities of the heart were full; the liver was of a purple color and the gall-bladder distended with bile; the brain and its membranes were turgid and there was much bloody serosity in the ventricles. Analysis discovered the existence of nitrobenzol in the brain and stomach."

The two Massachusetts General Hospital cases (W. M., No. 236170 and No. 236173) were both typical. They were young men who, in the course of a drinking party on April 13, 1920, bought six bottles of Jamaica ginger from a stranger. Both agreed that this ginger did not taste like ordinary ginger but was drinkable, so

that they partook freely of it. On subsequent analysis the liquid was found to contain a high percentage of nitrobenzol.

In about three hours after beginning on the first bottle one man began to have generalized headache, nausea, and blurring of vision. He thought that he fell on the sidewalk and remembered nothing further until he woke up in the hospital. The other man, at about the same time, began to feel dizzy and nauseated. He did not lose consciousness but came to the hospital with his friend.

At entry both men were of a steel gray-blue color, the unconscious man looking practically dead while his companion was of a ghastly color but in reasonably good shape. There was nothing else especially notable except that neither man excreted any urine for at least six hours after entry to the hospital. The stomachs of both men were washed out at once. The sicker man was bled 100 c.c. of blood and transfused with 600 c.c. of normal blood. In the middle of transfusion he suddenly woke up and appeared normal. The second man was also transfused, but with less dramatic effect. Both men, however, felt perfectly well on the following day and made normal recoveries, except that the more seriously poisoned man developed a mild, uncomplicated pneumonia.

The following laboratory studies were completed in both cases and are tabulated on page 544.

The most striking features in these tables are the hemoglobin figures. As can be seen the oxygen capacity of both bloods on the first observation was markedly reduced, in one case being only 6.2 volumes per cent. This figure approaches that obtained in one of Filehne's dogs, which was alive with an arterial blood having less than 1 volume per cent. of oxygen. The total hemoglobin in our 2 cases was not reduced, however. The fact that methemoglobin was not detected by spectroscopic examination suggests that a large proportion of the hemoglobin was changed to Filehne's nitrobenzol hemoglobin. This combination, in turn, was an easily destroyed compound as demonstrated by the blood analysis made twenty-four hours later. By this time the appearance of both patients was much more nearly normal and the bloods showed no diminution in their total hemoglobin, oxyhemoglobin or oxygen capacity. All cases, however, do not react this way, as many have been reported with unquestioned methemoglobinemia.

The leukocytosis which developed in one case has been described as occurring commonly in nitrobenzol-poisoning by Massini,[14] but can scarcely be due to rapid blood destruction according to his opinion.

As both cases were anuric for six hours after entering the hospital it is of possible significance that the phenolsulphonephthalein test

[14] Deutsch. Arch. f. klin. Med., 1910, ci, 72.

of one case should have only 20 per cent. forty-eight hours later. It is conceivable that nitrobenzol caused an acute toxic nephritis.

CASE I (NO. 236170) A.

	Blood.							
Date, 1920.	Red count.	White count.	Smear.	Hemoglobin, gms. per 100 c.c. blood.	Oxyhemoglobin, gms. per 100 c.c. blood.	O_2 capacity venous blood volume, per cent	Methemoglobin (spectroscope).	Urine.
April 13	5,072,000	40,000	Neg.	14.5	4.8	6.2	Not present.	
14	5,080,000	18,000	Neg.	15.2	14.9	19.9		
15	.....	...	...	...	...	...	...	High colored; contains para-amido-phenol; phenolsulphonephthalein excretion 20 per cent. in two hours; total nitrogen in twenty-four hrs. 14.3 gm.; total urea nitrogen in twenty-four hours 12.2 gm.; total ammonia nitrogen in twenty-four hours 1 gm.; total acidity including ammonia as $^{N}/_{10}$ acid in twenty-four hours 832 c.c.
20	5,008,000	10,800	Neg.					

CASE II (NO. 236173).*

	Blood.							
Date, 1920.	Red count.	White count.	Smear.	Hemoglobin, gms. per 100 c.c. blood.	Oxyhemoglobin, gms per 100 c.c. blood.	O_2 capacity venous blood volume, per cent.	Methemoglobin (spectroscope).	Urine.
April 13	4,204,000	10,800	Neg.	13.8	6.2	8.9	Not present.	
14	4,008,000	7,000	Neg.	15.2	14.9	19.9		
15	.....	...	...	...	...	...	...	High colored; contains para-amido-phenol; phenolsulphonephthalein excretion 40 per cent. in two hours.
20	5,040,000	10,800	Neg.					

* The total hemoglobin was determined by Stadie's[15] method. The oxyhemoglobin was determined from the oxygen capacity by Van Slyke's[16] method. We are obliged to Dr. W. Denis for recognizing para-amido-phenol in the urine.

[15] Stadie: Jour. Biol. Chem., 1920, xli, 237.
[16] Van Slyke: Jour. Biol. Chem., 1918, xxxiii, 127.

The high-colored, almost black urine excreted by these cases was probably due to para-amido-phenol. Meyer[17] also recognized it in a case which he reported. There was nothing remarkable in the nitrogen metabolism on the one case studied nor was there any significant increase in the titratable acidity of the urine.

It so happens that the cases recently reported in America have been mild, although Donovan has laid stress upon the fact that nitrobenzol may prove a fatal poison. The literature on the subject, moreover, contains so many reports of fatal cases that due emphasis should be laid upon the mortality of 32 per cent. in the 47 cases reported in 1883 by Grandhomme and the mortality of 21 per cent. in the group of 15 cases which Adams[18] discussed before the Association of American Physicians in 1912. Therefore, poisoning from nitrobenzol is a serious and often fatal condition.[19]

On the whole, nitrobenzol is by no means a new or rare form of poisoning but is of academic and clinical interest because of the effect it has upon the blood. Cases made ill by it in the past have absorbed it through the skin, by mouth and by inhalation; many accidental cases have occurred although this poison appears to have been less dangerous to those who handle it in their daily work than to those who have been poisoned through carelessness, curiosity, or the desire to commit suicide or abortion.

The symptoms and clinical picture of nitrobenzol poisoning are due to the fact the blood loses its function of transporting oxygen. Whether nitrobenzolhemoglobin methemoglobin or both are constantly formed is uncertain. In any event, cases of nitrobenzol-poisoning complain of the gradual onset of nervous and digestive symptoms going on to coma and death and become a characteristic blue-black color. The blood of such cases shows no change in the total amount of hemoglobin while the oxygen capacity of the blood is remarkably diminished. The urine is almost black in color and contains para-amido-phenol.

The changed hemoglobin, as a rule, returns to normal hemoglobin quickly, so that oxygen can again be carried to the body cells in a short time. This fact probably explains why cases which look extremely sick can recover with surprising rapidity.

There is no specific or antidotal treatment for this form of poison-

[17] Berl. klin. Wchnschr., 1905, xlii, 1353.

[18] Tr. Assn. Am. Phys., 1912, xxvii, 503.

[19] Since this paper was written, Dr. D. L. Edsall has called our attention to a fatal case of nitrobenzol-poisoning which came to the Massachusetts General Hospital in 1918. We are obliged to Dr. G. R. Minot for the following details in regard to the case: The patient, a man, aged forty-five years, was cleaning a railroad car with fluid which contained nitrobenzol. In some manner he broke the container so that its contents spilled over the lower half of his abdomen, soaking his clothes below the thorax. When he reached the emergency ward of the hospital, approximately forty-five minutes after the accident occurred, he was totally unconscious, intensely cyanosed and died in a short time. The impressive fact in relation to this case was that nitrobenzol absorbed through the skin caused death within almost a few minutes after exposure.

ing. Any nitrobenzol, however, which has not been absorbed in a given case should be removed from contact with the body as completely and quickly as possible. Bleeding and transfusion seem logical therapeutic procedures for the most severe cases.

A NEW INTESTINAL TUBE WITE REMARKS ON ITS USE IN A CASE OF ULCERATIVE COLITIS.

By Max Einhorn, M.D.,

PROFESSOR OF MEDICINE AT THE NEW YORK POST-GRADUATE MEDICAL SCHOOL, NEW YORK.

About a year ago I[1] described an intestinal tube by means of which it is possible to reach the entire small intestine and also the large bowel for diagnostic and therapeutic purposes. The tube having a length of 15 to 20 feet, and being quite thin (8 mm. circumference), does not permit its employment for aspiration purposes. Inasmuch as it is not permissible to have more than 60 cm. of the tube enter the digestive tract, before the capsule end has passed the pylorus, it is absolutely essential to demonstrate by the roentgen ray the position of the tube before allowing its further passage into the alimentary canal. This is a great disadvantage, making the clinician absolutely dependent in his work upon the roentgen-ray apparatus. The handling of the very long tube is another cumbersome drawback. Ultimately the length of the intestine being subject to great variations the intestinal tube had to have a length enough to fit all occasions, thus frequently exceeding the actual need of the individual case.

In order to obviate these drawbacks I have constructed a "jointed intestinal tube." It consists of the usual duodenal tube, the distal end of which is provided with a metal fitting and a female thread. Several 1-meter long tubes of the same caliber as the duodenal tube (8 F.) are each provided with tiny metal fittings at both ends, on one side having a female and on the opposite side a male thread. All the threads are of exactly the same size and each male fitting can be joined with a female thread. The distal end of the new tube is formed by a piece of rubber tubing (20 to 25 cm. long and about 20 F. caliber), containing on its proximal side a metal fitting with a male thread and on its distal side a stopcock. This distal end-piece can be attached either to the first duodenal tube piece or to each subsequent length of tubing added, thus forming a "jointed tube." (See Fig. 1.)

The jointed intestinal tube[2] permits aspiration at one and some-

[1] Einhorn, Max: An Intestinal Tube, New York Med. Jour., September 13, 1919.

[2] The jointed intestinal tube can be obtained at Geo. Tiemann & Co., 107 East 28th Street, New York.

times 2 meter-lengths, thus making it possible for the clinician to ascertain the position of the capsule in the duodenum and thus facilitates its introduction. Each subsequent length of tubing is added when its predecessor has entered the digestive tract. In order to avoid curling up of the tube in the stomach it is essential not to allow too much tubing to enter the stomach while eating and to ascertain the position of the tube before adding another length. This is done by pulling the tube a short distance from the mouth, 2 or 3 inches. If there is no resistance felt the tube is curled in the stomach. If a resistance is experienced the probability is that there is no curling. At this point a roentgen ray is advantageous, as it shows the course of the tube more exactly. A roentgen ray will also be required to decide whether the cecum has been reached, whenever it is necessary to do so, in order to apply treatment to the colon.

FIG. 1.—The jointed intestinal tube.

By means of the jointed intestinal tube the following case of probable ulcerative colitis has been successfully treated by lavage of the colon from above.

January, 1920. S. G., about forty years old, has been suffering for the last two years from severe diarrhea. Colicky abdominal pains are frequently present, especially before a bowel movement. Patient has lost considerably in weight and strength.

Present Condition. Examination of the chest does not reveal anything abnormal. The abdomen is slightly bloated, the liver a trifle enlarged and there is a distinct tenderness all over the colon on slight pressure. The gastric contents show: HCl = +; Ac = 56; no blood. The stool shows presence of starch, mucus and blood. The bead test reveals: beads appear in the stool after twenty-six hours; three-fourths of a potato, half fat, trace of thymus (no nuclei) present. Patient looks pale and complains of abdominal discomfort, lack of appetite and disturbed sleep. On an average he has six to eight movements during the day and four to six during the night.

Patient was then treated by me at the Lenox Hill Hospital for

a few weeks with tannin-agar, taka-diastase and a regulated diet, also bowel irrigations through the rectum, with some benefit, and sent to the mountains, where he stayed about two months. During May, 1920, patient returned to the city with an exacerbation of the previous symptoms.

A reëxamination showed practically the same findings as stated above. The diagnosis appeared to be severe ulcerative colitis. Inasmuch as the usual methods of treatment failed to accomplish the desired result, it appeared worth while to try washings of the bowel from above. Up to now for this purpose an appendicostomy or cecostomy would have to be first performed. With the intestinal

FIG. 2.—V 21, 1920. Roentgen-ray photograph of patient S. G., with the intestinal tube in the digestive tract. The capsule end of the tube is visible in the lower part of the duodenum.

tube at hand it was decided to try lavage of the colon from above by means of this instrument, thus obviating, if possible, the operation. Accordingly the jointed intestinal tube was introduced on May 20, 1920. As soon as the first part entered the duodenum (Fig. 2) the second joint was attached. On May 23, the third joint was added. A roentgen-ray picture showed the capsule end of the tube in the cecum (Fig. 3). Lavage of the intestine with a weak solution of carbonate of calcium (0.5 per cent.), employing a quart twice daily, was instituted as soon as the second joint had been attached, and kept up for about two weeks. Patient was nourished in the usual way by the mouth, partaking of the customary anti-

diarrheic diet. Soon after instituting this regimen the patient felt considerably relieved. The abdomen was not bloated, his appetite grew better and there were three or four movements daily. About a week later there were two or three movements daily, well formed, not containing any blood or mucus.

Wishing to have a roentgen-ray picture of the intestinal tube demonstrating the position of the entire intestinal tract, including the large bowel, a fourth joint was attached on the evening of June 5, 1920. The following day the capsule end of the tube appeared in the stool, hanging outside of the rectum. Desiring to demonstrate the location of the entire instrument with the capsule in the

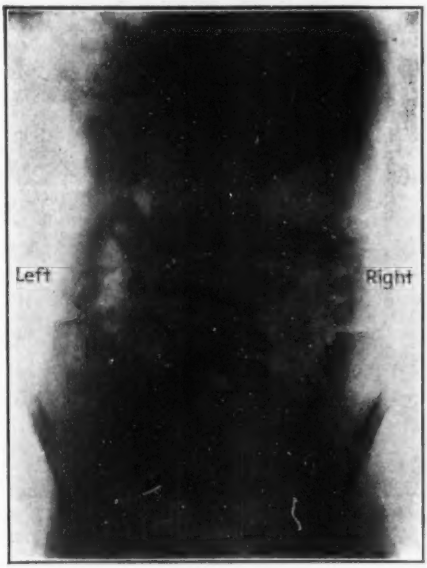

FIG. 3.—V 24, 1920. Roentgen-ray photograph of same patient shows the capsule end of the tube in the cecum.

digestive tract, I pushed it back into the rectum and had the patient roentgen rayed the following day, after injecting a bismuth mixture through the intestinal tube (Fig. 4).

In order to rid the patient of the instrument, the distal part with the stopcock was detached. The tube was tied tightly at the lips and allowed to slip into the stomach. Two days later (June 9) the whole tube appeared in the stool. During the entire time of treatment the patient experienced no pain or discomfort from the presence of this foreign body in his digestive tract.

It is thus evident that the intestinal tube can be used with advantage whenever this mode of treatment appears to be indicated.

In the case just reported the intestinal tube eliminated an operation—cecostomy or appendicostomy—which in similar instances is frequently done and effected great improvement—if not a cure.

Another point of interest regarding the penetration of the intestine by tubes is the rare event described by Dr. Palefsky,[3] when the capsule-end of the duodenal tube (about 1 meter long), although the distal part was still at the lips, appeared through the rectum of a patient at the Montefiore Home. Palefsky explains this as string-

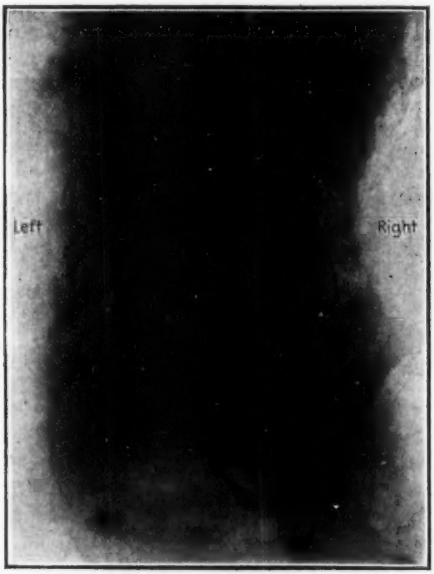

FIG. 4.—VI 7, 1920. Roentgen-ray photograph of same patient after filling the intestinal tube with a thin emulsion of bismuth. The whole course of the small intestine and colon down to the rectum is made visible by the tube. The capsule end is noticeable in the rectum.

ing up of the intestine over the tube. I have never seen a similar occurrence with the duodenal tube. Whether Palefsky's explanation is correct or whether there was a communication between the beginning of the small intestine and the colon (fistula), thus shortening the route is difficult to say. At any rate the duodenal tube cannot replace the intestinal tube, when in some instances a special diagnosis or treatment of the small intestine or colon is demanded. The jointed intestinal tube is, therefore, deemed of value.

[3] New York Med. Jour., April 18, 1912.

NOCTURNAL POLYURIA.

By Joseph H. Barach, M.D.,
PRESBYTERIAN HOSPITAL, PITTSBURGH, PA.

Nocturnal polyuria is a term designating an abnormal increase in the amount of night urine.

In seeking an explanation of its occurrence I attempted a review of the literature on nephritis which yielded no satisfactory explanation for the pathologic physiology of this symptom, and, above all, it revealed the fact that no special study of nocturnal polyuria has been made.

In health the amount of urine excreted during the hours of 8 A.M. to 8 P.M. is two or three times as much as is excreted from 8 P.M. to 8 A.M. When nocturnal polyuria exists the amount passed during the night hours exceeds that of the day, or it is habitually more than 400 c.c.

Here then is an interesting problem, Why should the normal relationship of function be reversed? Under what conditions does it occur? What are the peculiarities of the night urine? What is the diagnostic and prognostic significance of nocturnal polyuria?

Present Study. To this end I made a survey of 100 cases of subacute and chronic nephritis. These cases occurring in my private practice afforded me the opportunity of weekly observation. In some of them I made observations uninterruptedly for more than a year.

Methods. To establish the diagnosis in a case of nephritis aside from a study of the usual clinical evidences, when circumstances warrant, we make quantitative blood analyses for urea nitrogen, creatinin, blood sugar and chlorides. The phenolsulphonephthalein test is carried out both intramuscularly and intravenously. By this method we attempt to determine the tissue factor, *i. e.*, the rate of absorption by the tissues as well as the ability of the kidneys to eliminate the dye substance.

The urinalysis consists of a separate collection of the day and night urine from 8 A.M. to 8 P.M. and from 8 P.M. to 8 A.M. In these specimens, aside from the usual clinical and microscopic examinations, we make quantitative analyses of urea, chlorides, total acidity and ammonia. When the plasma chlorides are to be estimated a specimen of urine is obtained at the time when the blood specimen is taken for a quantitative chloride estimation.

While all this may sound formidable it is indeed very simple. The greatest tax is upon one's willingness to carry it over prolonged periods. Certainly, it is well worth doing because if properly interpreted much light is thrown on the patient's condition and it is the very best guide in our therapeutic efforts.

The urea estimation serves to indicate the protein metabolism; the chlorides indicate the salt intake and output, and the total acidity and ammonia indicate the acid equilibrium.

Cases Studied. In a survey of the entire series of cases upon which these observations were based, I find that from our present viewpoint they may be divided into three groups:

Group I includes those patients who come to the physician with no clinical symptoms of nephritis, and as judged by the usual methods, they show no evidences of impaired renal function. In most of them the time of onset of nephritis is unknown. The only evidences of an existing nephritis is the constant presence of albumin and casts. These cases show no nocturnal polyuria.

Group II includes those patients who have at least some unmistakable symptoms of early nephritis. These patients frequently show evidences of wear and tear. They give a history of periodic headaches, and at times we find the blood-pressure at the upper normal limit. Some of the patients in this group are anemic and present a picture of asthenia. In these cases the night urine is usually more than 400 c.c., but it does not always exceed the amount of the day urine.

Group III includes those patients in whom the diagnosis can be made with certainty on the clinical symptoms alone. They have enlarged hearts arterial changes; they suffer with nocturnal headaches, insomnia, dyspnea on exertion and they lack endurance. Usually they present a severe grade of arterial hypertension. It is in this type of case that we find an established nocturnal polyuria. The laboratory findings show defective renal function, as it is reflected in the blood analysis and by the various urinary examinations.

The Urinalysis in Nocturnal Polyuria. The amount of night urine may be from one and a half to four times that of the day urine. The color is darker in the day specimen and lighter at night. The specific gravity is high in the day specimen and low in the night specimen. The total solids eliminated is greater during the night when nocturnal polyuria is marked. These are the usual characteristics, and all of them are the reverse of the normal.

The Urea. In cases in which nocturia is present the urea concentration is greater during the day, but the total output is greater during the night. This is the reverse of that which is found when the kidneys are normal or but slightly damaged. It is an established fact that only the very seriously injured kidney will fail to eliminate urea or show a fixation of the urea elimination. From all my observations I should say that the ability of the kidneys to concentrate or eliminate urea is in no apparent way the cause of nocturnal polyuria.

The Chlorides. When nocturnal polyuria is marked the chloride concentration is higher at night, and since the volume is larger

the chloride output is also greater at night. In the normal person the chloride output is lower at night. The observations in this entire series show a distinct parallelism in the water and salt elimination, both tending constantly in the same direction. There is plenty of clinical evidence to show that polyuria is at times a result of chloride stimulation.

Total Acidity. The hydrogen-ion concentration as estimated by titration in the presence of neutral K oxalate and adding the ammonia value shows a higher acidity in the night urine when nocturnal polyuria is present. In the normal individual the total acidity is greater in the day specimen.

Concentration of the Urine. The one explanation which is most frequently offered for the occurrence of nocturnal polyuria is inability of the kidneys to concentrate urine. Most of my cases of nocturnal polyuria showed a distinct variation from time to time, the urea and chloride values often reaching quite a high point. On the other hand if nocturnal polyuria were due to inability to concentrate, both the day and night urine should be of the same low concentration. This, as all my observations show, is not the case at all. I am inclined to believe that nocturnal polyuria occurs because the diseased kidneys cannot eliminate water as well during the day as in the night.

Summary of the Urinary Findings in Nocturnal Polyuria. On all points excepting the higher concentration of urea during the day hours the night urine presents the characteristics of the day urine and the day urine resembles the normal night urine.

Therefore, when nocturnal polyuria is present we observe an almost complete reversal of function.

Blood Chemistry in Nocturnal Polyuria. We paid special attention to the blood chlorides in a series of cases in which nocturnal polyuria was a permanent symptom. In comparing the blood plasma chloride and urinary chlorides of these patients our findings seemed too indefinite for any reasonable deductions. The same may be said of blood sugars, creatinin and urea nitrogen.

Before offering an explanation of nocturnal polyuria let us summarize our evidence up to this point. In nocturnal polyuria the quantitative chemical analysis is the reverse of normal. The chief characteristics—those which are always present—are increased water output, higher acid concentration and output and lower urea concentration, but greater output in the night specimen.

Nocturnal polyuria occurs in subacute and chronic nephritis. It occurs when the blood-pressure is normal, but is more marked in arterial hypertension.

There are many possible factors which might influence the amount and character of the night urine, and I wish to discuss a few of the more obvious ones.

Foods and Liquids Ingested. Nocturnal polyuria occurs with the same regularity among patients who take their dinners at noon as those who take theirs in the evening. Neither the food nor the liquids taken during the evening are the cause of nocturnal polyuria, although much liquid taken in the evening does exaggerate this symptom.

Physical Exertion. Nocturnal polyuria occurs in patients who are at their usual occupations and in those who are away from their work. From these observations it appears that the total amount of physical exertion during the day is not the important factor. It is the variation between the exertion of the day and the relaxation of the night which undoubtedly does make the night a more favorable time for renal function when the kidneys have not fully accomplished their work during the day.

Blood-pressure. Nocturnal polyuria is most marked in nephritis with high blood-pressure. It occurs also when the blood-pressure is low. In borderline cases nocturnal polyuria disappears and the normal day and night proportions are reëstablished when the previously high blood-pressure falls to normal. The alteration of pulse-pressure during the hours of sleep is probably the important factor in creating a more favorable condition for urinary filtration.

I see no reason why the renal epithelium should secrete better at night, but there seem to be many reasons why the altered renal circulation at night should prove more favorable to increased water elimination. Doubtless it may be that the unexcreted urinary substances of the day also act as a renal stimulant.

Posture. When a patient who has an established nocturnal polyuria goes to bed for a week or two the nocturnal polyuria continues irrespective of the fact that he is in the horizontal posture all of the twenty-four hours. During this bed period the nocturnal polyuria will be less marked, but the increased night urine will persist.

This brings us to what is perhaps the most important factor in the production of nocturnal polyuria.

Sleep. Up to this point our observations lead us to believe that it is not the heavy evening meal, nor the amount of physical exertion of the preceding day, nor the presence or absence of arterial hypertension, nor the horizontal posture which produces nocturnal polyuria. Having set these aside the one remaining factor which will come into our discussion is sleep. During the hours of sleep, when the muscular system is in a state of relaxation and the respiratory and circulatory systems are in a state of comparative rest, it must be that whether it is the lower pulse-rate or altered pulse-pressure, or whatever other alterations may occur in the mechanics of the renal circulation, the conditions are more favorable for renal filtration.

Summary and Conclusions. Nocturnal polyuria is a highly diagnostic symptom of an established subacute or chronic nephritis. It occurs independently of arterial hypertension. The quantitative

analyses show a complete reversal from the normal in the amount of work accomplished by the kidneys during the day and night periods.

Observations upon patients having nocturnal polyuria show that it is not the result of heavy evening meals, physical exertion, arterial hypertension nor the horizontal posture. The most probable cause seems to be found in the physiologic adjustments in circulation incidental to sleep. The evidences gathered in these observations suggest that nocturnal polyuria is primarily a manifestation of increased elimination of water because of a more favorable state of the renal circulation and that the increased elimination of salts is coincidental rather than causative.

THE WHITE ADRENAL LINE (SERGENT); ITS CLINICAL SIGNIFICANCE.

By Willard E. Kay, M.D.,
San Francisco, California,
and
Samuel Brock, M.D.,
New York, N. Y.

Since the appearance of Sergent's American article[1] directing attention to his white adrenal line in 1917, considerable clinical application has been made of it in this country, to judge from the increasingly frequent references to it in the current literature.

This line is a blanching of the skin following light stroking by a blunt object, such as by the back of the finger-nail or the eraser at the end of a pencil. The subject assumes the recumbent position, with abdomen exposed for at least twenty minutes, and then a figure, such as a triangle or rectangle, is stroked lightly on the skin of the upper abdomen. Shading the part from bright light is of aid in the perception of the line. In about ten seconds a pure white band varying in intensity and unmixed with any element of red appears; it lasts from three to fifteen or more minutes.

Sergent definitely ascribes this phenomenon to a state of hypoadrenia.

Our interest in this remarkable skin reaction was aroused by studies made on a case of dystrophia adiposogenitalis[2] in which the line was present in a very pronounced degree. Curiously enough, while the line disappeared promptly following the administration of adrenalin subcutaneously, it reappeared quite quickly (in twenty

[1] The White Adrenal Line: Its Production and Diagnostic Significance, Jour. Endocrinol., January, 1917, i, 18.

[2] Unpublished: To be reported later. (Arch. Int. Med., 1921.)

minutes), in face of the fact that the general effects of adrenalin (tremor, cardiac palpitation, throbbing of vessels, increased pulse and heightened blood-pressure) were marked and persisted over a prolonged period (four hours).

These findings, inconsistent with Sergent's explanation of the line, led us to investigate this phenomenon and the factors which influence it in a series of 255 cases.

In eliciting this phenomenon the directions set forth by Sergent were followed in every detail.

Of the 255 instances, comprising all types of disease and a series of normals, a white line was obtained in 58 per cent.; a red line (tâche cérébrale) in 9 per cent.; an indifferent type of line as described by Tracey[3] in 33 per cent. The latter is a deepening of the normal skin tint, with a whitish or reddish admixture, or a red quickly followed by a white band.

For purposes of comparison three grades of intensity were recorded, namely, one plus, two plus and three plus. Of the 145 instances (58 per cent. of total) of white lines, 14½ per cent. were three plus, 38½ per cent. were two plus and 47 per cent. were one plus.

It is interesting to note that the white line was the one most frequently found.

No difference was found in the response of the two sexes.

All types of disease were represented in this series (Table I).

Although the series analyzed is not a very large one the large number of normals revealing the line—58 per cent.—and the fact that 43 per cent. of the hypertension cases exhibited it, are of special interest.

It will be noted that the line was found in all instances of scarlet fever, hypopituitarism and in two cases of scleroderma.

Scarlet fever patients *quite constantly* reveal this phenomenon, a point emphasized by Moltchanow and Lebedeff.[4]

The typical white line response elicited in the skin, flushed with the exanthem of scarlet fever is not to be confused with the familiar momentary blanching produced by pressure of the hand. This blanching is very speedily followed by the return of the flush, whereas the white line appears after an "incubation period" of usually five to ten seconds, attains a maximum and slowly fades out.

After recovery from scarlet fever and the disappearance of the rash, this line disappears in a certain number of the cases.

Unfortunately we were unable to study a series of frank Addison's disease.

[3] The Normal Reaction of the Skin to Stroking, Boston Med. and Surg. Jour., 1916, clxxv, 197. Correlations Between the Systolic Blood-pressure and Reflex Vasoconstriction (Anemic Dermography), Boston Med. and Surg. Jour., 1917, clxxvi, 15.

[4] Vagotonus and Sympathicotonus in Scarlet Fever in Children, Roussky Vratch, Petrograd, 1916, xv, 457; Abstracted in Jour. Endocrinol., January, 1917, i, 92.

Nor was it possible to correlate the presence of this line with any particular type of individual, *i. e.*, with respect to vasomotor system and nervous make-up, except that it seemed quite frequent in those with a hypertonic vegetative nervous system. As regards its relationship to endocrine disorders, its ascribed dependence upon a state of hypo-adrenia was certainly not demonstrated. It was not found that adrenalin-sensitive individuals bore any constant relationship to it, although they very frequently revealed it.

TABLE I.—THE INCIDENCE OF THE VARIOUS LINES IN DIFFERENT DISEASES AND NORMALS.

Disease.	Red.	Indefinite.	White.	Per cent. white.
Normals[1]	1	12	18	58
Cardiovascular and cardionephritic	4	8	10	45
Anemias (including pernicious)	1	3	1	20
Neurological:				
Organic	2	11	18	58
Epilepsy	1	2	4	68
Functional and psychiatric	0	11	11	50
Tuberculosis (pulmonary)	3	4	18	72
Hypertension	3	5	6	43
Endocrine:				
Hyperthyroid	3	1	6	60
Hypothyroid	1	0	0	
Hypopituitarism	0	0	4	100
Hyperpituitarism	0	0	1	
Hypo-adrenia	0	2	0	
Eunuchoid	0	0	1	
Metabolic	1	6	1	12
Infectious	4	8	21	63
Scarlet fever	0	0	4	100
Measles	0	1	3	75
Neurocirculatory asthenia	2	0	3	60
Skin (miscellaneous)	0	3	5	62
Scleroderma	0	0	2	100
Arthritis, chronic, including arthritis deformans	3	5	2	20
Hypernephroma	0	1	0	

On the other hand, of particular significance has been the study of the age incidence (Chart I). It will be noted that the greatest incidence occurs between the ages of ten and thirty years. In fact the frequency of this line in young adults has been quite surprising; its infrequency in the extremes of life a matter worthy of attention.

Not only is this line most often found during young adult life, but it is met with most frequently in those with a normal blood-pressure. Infants with low pressure rarely have it. Yet a high systolic pressure, whether induced by the subcutaneous injection of tyramin or the result of hypertension does not preclude its presence; we have seen it in three individuals with systolic pressures of 230 mm. and over. No relation was noted to diastolic or pulse-

[1] The majority of normals were young adults.

pressure variations. Pulse-rate has been found to have no bearing upon its presence.

On the other hand, it seemed that those individuals possessing a soft, doughy type of skin were especially likely to have the line.

The influence of various drugs, mechanical factors, etc., has been studied.

When adrenalin or pituitrin (posterior lobe hypophysis) are administered subcutaneously in doses of 0.6 to 1 c.c. the line disappears for usually a period of fifteen to thirty minutes, following which it reappears and quickly attains its former maximum. Not infrequently the other general effects of adrenalin (tremor, throbbing of vessels, cardiac palpitation, heightened blood-pressure, etc.)

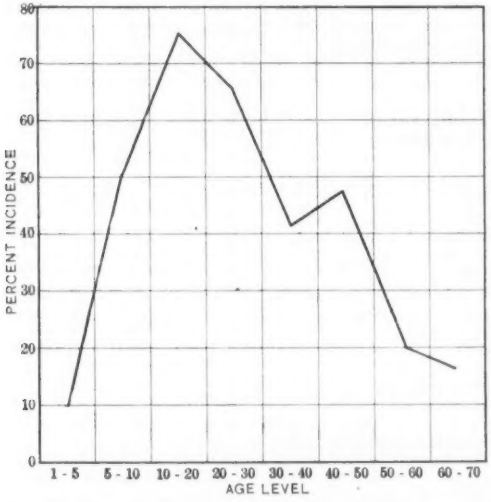

CHART I.—The percentage incidence of white line at various age levels.

continue over a considerably longer period than that occupied by the disappearance of the line. A characteristic example of this is herewith detailed (Table II).

This apparent inconsistency is to be explained, we believe, on the assumption that both adrenalin and pituitrin cause the disappearance of the line, solely by their peripheral vasoconstrictor action and not through any general effects.

In the same way the local application of heat and cold produce the disappearance of the line.

That the increase in blood-pressure has nothing to do with the line's presence or absence is again demonstrated by the action of tyramin, a drug which has been shown to produce extraordinary

rises of blood-pressure through splanchnic vasoconstriction and cardiac stimulation.[6 7]

This drug in doses of 60 to 80 mgm. has conditioned rises of 60 to 100 mm. pressure without affecting the line.

TABLE II.—THE EFFECT OF ADRENALIN ON THE WHITE LINE IN A CASE OF HYPOPITUITARISM. (ADVANCED DYSTROPHY ADIPOSO-GENITALIS).

	Pulse.	Blood-pressure.		
		Systolic.	Diastolic.	
Before administration	80	120	80	
Epinephrin, 1 c.c. 1 to 1000 solution(hypodermic):				
5 minutes later	104	140	80	Tremor fairly marked; heart thumping; palpitation marked; patient moderately pale; respiration rapid; patient complains of feeling very nervous; disappearance of white adrenal line.
10 minutes later	112	140	80	White adrenal line gradually reappearing and becoming more marked; marked tremor; palpitation of heart; nervousness continuing.
15 minutes later	112	145	80	White adrenal line well marked, notwithstanding a maintenance of the heightened blood-pressure; tremor, etc., still marked.
25 minutes later	115	140	80	White adrenal line still marked; blood-pressure still high.
1 hour 30 minutes later	110	145	88	White adrenal line marked; tremor; palpitation; throbbing and nervousness marked.
2 hours 30 minutes later	120	135	88	White adrenal line marked; palpitation and throbbing of vessels still fairly marked; patient still complains of nervousness.

Pilocarpin in doses of 6 to 8 mgm. seemed to accentuate the line in some cases; in others it seemed to have no effect (Table III).

In a group of 20 cases the effect of acute fatigue was noted. Running for varying distances, 150 to 300 or more yards, until considerable dyspnea and fatigue were manifest, was used. In

[6] Hewlett, A. W.: The Action of Tyramin on the Circulation of Man, Arch. Int. Med., 1918, xxi, 411.

[7] Hewlett, A. W., and Kay, W. E.: The Effect of Tyramin on Circulatory Failure during Infections and during or after Operations, Jour. Am. Med. Assn., 1918, lxx, 1810.

no instance was any appreciable change noted in the line, nor were we able to produce this line by this or any other method in an individual not possessing it before.

TABLE III.—THE EFFECT OF PILOCARPINE ON THE WHITE LINE IN A CASE OF MILD HYPOPITUITARISM.

	Pulse.	Blood-pressure.		
		Systolic.	Diastolic.	
Before administration	70	135	80	Moderate white line.
Pilocarpin, 8 mgm., by hypodermic:				
10 minutes later	80	135	75	White line more marked.
30 minutes later	80	130	70	A feeling of warmth noted; white line still marked.
50 minutes later	80	130	70	No perspiration; no special symptoms; white line marked on abdomen and face.

When the line is elicited in the standing position it is less prominent or absent.

We were unable to determine any changes in the line conditioned by psychic disturbances.

While the intensity of the line varied slightly at different times during the period of observation, no individual was found in whom the line appeared, having been absent, or in whom it disappeared when once present.

Tracy[8] has postulated an attractive hypothesis, attempting to explain the appearance of the white and the red lines in different individuals, on the basis of a theory which is adapted from the work of Eppinger and Hess on Vagotonia.[9]

The theory may be formulated as follows:

1. Stimulus affecting the sympathetic nerve endings + adrenalin, acting on smooth muscles of vessels produces vasoconstriction (white line).

2. Stimulus affecting the autonomic nerve endings + hormone "X" ("autonomyn"[10]), acting on smooth muscle of vessels produces vasodilatation (red line).

This conception would imply that the white line is a manifestation of sympathicotonia, as Eppinger and Hess believe, whereas the red line is due to vagotonia.

Tracy[11] has even gone so far as to state that "reflex vasoconstric-

[8] Loc. cit.

[9] Vagotonia, a Clinical Study in Vegetative Neurology, Nervous and Mental Diseases Monograph Series No. 20, 1917. (Translated by Drs. Kraus and Jelliffe), Nerv. and Ment. Dis. Pub. Co.

[10] A theoretical hormone elaborated by the thyroid gland, anterior lobe of the hypophysis and the thymus.

[11] Loc. cit.

tion (anemic dermography) measures the adrenin content in the blood stream."

It will be noted that this conception is diametrically opposed to Sergent's belief, which would have the white line reflect a paucity of adrenalin in the blood stream.

Conclusions. 1. From the study of a series of 255 cases of a variety of diseases and normals, upon which numerous pharmacologic and other tests were performed, we feel justified in asserting that the so-called white adrenalin line of Sergent is a local vasomotor reflex, resident in the skin, bearing no direct relationship to adrenal gland activity.

2. The reasons for postulating the above are: (*a*) Its independence of blood-pressure, acute fatigue and other signs of hypo-adrenia; (*b*) its frequent occurrence in normals and in a variety of diseases unassociated with hypo-adrenia; (*c*) its reappearance in the face of persistent general manifestations of adrenalin subcutaneously administered; (*d*) its peculiar association with scarlet fever.

3. It would appear that the state of the vasomotor system which allows of its best exhibition is found in young adults of either sex, and especially in the exanthem of scarlet fever.

4. On the basis of the above series it may be stated that this line has not the clinical significance attributed to it.

5. In spite of the various hypotheses evolved regarding it, further work seems necessary to establish the exact physiologic mechanism of this remarkable vasomotor phenomenon.

Our thanks are due to Drs. Harlow Brooks, Sigmund Wachsmann and Robert Wilson for valuable advice and privileges granted. Through their courtesy we were able to study cases in the wards of the City Hospital (Blackwell's Island, N. Y.), Montefiore Home and Hospital and the Willard Parker Hospital, N. Y.

CHOLESTEROL IN CEREBROSPINAL FLUID.

By A. Levinson, M.D., Loraine L. Landenberger, B.S.

and

Katharine M. Howell, M.D.,

Chicago, Ill.

(From the Sarah Morris Hospital for Children and the Nelson Morris Memorial Institute for Medical Research of the Michael Reese Hospital, Chicago.)

Recently some importance has been attached to the presence of cholesterol in cerebrospinal fluid by Pighini[1] and by Hauptmann.[2]

[1] Ueber den Cholesteringehalt der Lumbalflüssigkeit einiger Geisteskrankheiten, Hoppe-Seyler's Ztschr. f. physiol. Chem., 1909, lxi, 508.

[2] Eine biologische Reaktion im Liquor Cerebrospinalis bei organischen Nervenkrankheiten, Med. Klin., 1910, vi, 181.

In view of this claim and in view of the role of blood cholesterol in various diseases we have made a series of determinations of cholesterol in cerebrospinal fluid, with special attention to pathologic fluids.

Methods.—The method of Bloor,[3] with a few modifications, has been employed by us for quantitative determination and the method of Hauptmann[2] for qualitative determination. It should be noted here that although Hauptmann himself was not certain that the inhibition of saponin hemolysis by cerebrospinal fluid in some pathologic cases was due to the presence of cholesterol a comparison of the saponin with the Bloor method shows that with a few exceptions the two tests run quite parallel.

In the Bloor method the amount of fluid to be used for each test was naturally a question of great importance, as it was clear that cerebrospinal fluid could not contain as much cholesterol as blood contains.

After a series of experiments we found that whenever the cerebrospinal fluid contains cholesterol in appreciable amount, 3 c.c., the amount used for blood cholesterol will give a reading in the colorimeter. If 3 c.c. of fluid do not give a reading, 6 c.c. or even 10 or 15 c.c. of the same fluid will give no reading in the colorimeter. We therefore decided to take 3 c.c. as the standard amount of fluid, as one is usually able to spare this amount with ease. Whenever possible, however, 6 c.c. or more of the same fluid or of the same type of fluid were used as a check.

Three c.c. of the fluid which had been drawn by means of a spinal or ventricular puncture were measured into a 100 c.c. volumetric flask and ether-alcohol (1 to 3) added. The flask was heated to the boiling-point and set aside. After standing twenty-four hours to several days, ether-alcohol was added to the 100 mark, the contents filtered and 80 c.c. of the filtrate taken for the cholesterol determination. We found 10 c.c. of the filtrate, the amount used in the blood cholesterol method, insufficient for the determination of cerebrospinal cholesterol.

The filtrate was evaporated to dryness and the cholesterol extracted by chloroform and the chloroform extract concentrated to 5 c.c., which was then put into a 10 c.c. graduate, 2 c.c. acetic anhydride and 0.2 c.c. sulphuric acid added, shaken and put away for fifteen minutes in a dark place. The material was then compared with a standard of 0.5 mgm. of cholesterol in a Dubosecq colorimeter if the color of the cerebrospinal filtrate were sufficient to make a reading. If no color at all appeared the solution remained light yellow and we called it negative. If a greenish-yellow color appeared we designated it as a trace.

[3] The Determination of Cholesterol in Blood, Jour. Biol. Chem., 1916, xxiv, 227. The Determination of Cholesterol in Blood, Jour. Biol. Chem., 1917, xxix, 437.

The technic of the Hauptmann test used was as follows: Each time the test was performed the hemolytic unit of saponin was determined. Various samples of saponin tried were found to vary greatly in their hemolytic action, but the sample finally used caused hemolysis in a 1 to 10,000 dilution. The dosage of this dilution necessary to cause complete hemolysis of 0.5 c.c. of a 7 per cent. suspension of washed sheep erythrocytes in 0.85 per cent. saline was determined by adding increasing amounts of the saponin solution to the corpuscle suspension in a series of small tubes. The hemolytic unit of the 1 to 10,000 saponin solution was usually found to be 0.3 c.c.; occasionally it was 0.2 or 0.4 c.c. After the saponin unit has been determined, 0.8 c.c. of cerebrospinal fluid to be tested was set up with the required amount of saponin and 0.5 c.c. of 7 per cent. sheep red corpuscle suspension. Control tubes with normal cerebrospinal fluid (one known not to produce any inhibitory effect on saponin) and with normal salt solution were also set up. The results were read after ten minutes in the water-bath at 37° and again after twelve hours in the refrigerator. The setting up of the saponin test with a positive result is illustrated by the following table:

Tube 1. 1 to 10,000 saponin, 0.3 c.c.; normal cerebrospinal fluid, 0.8 c.c.; 7 per cent. sheep corpuscle suspension, 0.5 c.c. Result: Complete hemolysis.

Tube 2. 1 to 10,000 saponin, 0.3 c.c.; cerebrospinal fluid to be tested, 0.8 c.c.; 7 per cent. sheep corpuscle, 0.5 c.c. Result: Inhibition of hemolysis.

Tube 3. 1 to 10,000 saponin, 0.3 c.c.; 0.85 per cent. saline, 0.8 c.c.; 7 per cent. sheep corpuscle suspension, 0.5 c.c. Result: Complete hemolysis.

Results.—We have examined 168 fluids for cholesterol; 74 of these were examined quantitatively, and of these 52 were also examined by the saponin method. The rest of the fluids were examined only qualitatively by the saponin method. Our fluids divided themselves into six groups:

1. *Normal fluid*, including all fluids in which the Wassermann, Lange, cell count and globulin tests were negative. These include a variety of conditions, such as pneumonia, multiple sclerosis, amaurotic family idiocy, epilepsy and other cases in which irritation of the brain justified spinal puncture but the fluid showed no pathologic findings; 88 fluids of this type were examined. Of these 24 were examined both quantitatively and qualitatively and 64 only qualitatively.

2. *Luetic or Neurosyphilitic Fluid.* This includes all fluids in which the Wassermann and Lange reactions were found positive. Of these 25 fluids were examined both quantitatively and qualitatively and 28 fluids only qualitatively.

3. *Meningitic fluid*, including all forms of meningitis. There were 16 fluids in this group examined both quantitatively and qualitatively.

4. *Brain tumor* (4 cases) and *brain abscess* (2 cases). Of the brain tumor cases a positive diagnosis had been made in 3 and a probable diagnosis in 1. The fluid from 2 of the positive brain tumor cases and from the one suspicious case were examined both quantitatively and qualitatively; that from 1 positive case only qualitatively. The fluid from 1 case of brain abscess was examined both quantitatively and qualitatively and the other only qualitatively.

5. *Hemorrhage of the Brain.* Two cases, both examined by both methods.

6. *Ventricular Fluid.* Three cases, both methods being used in each case.

Normal fluid gave no reaction at all with the Bloor method, no matter whether 3, 6 or even 10 c.c. were used; only when 25 c.c. of fluid was taken for a test was there a trace of cholesterol present. Saponin hemolysis was not inhibited by the presence of normal cerebrospinal fluid.

Luetic fluid, with three exceptions, also gave no reading with the Bloor method nor was there any inhibition of hemolysis. Of the three fluids that contained cholesterol in appreciable amounts one was also meningitic in character. The two others were diagnosed merely as general paresis.

Of the fluid from cases of meningitis only three contained a sufficient amount of cholesterol to enable us to read it in the colorimeter, one of these also giving a positive Wassermann reaction. The rest of the fluids showed a greenish-yellow discoloration as the end reaction, which was taken to indicate the presence of a trace of cholesterol. There was not, however, a sufficient amount of cholesterol in them to allow a reading in the colorimeter. Saponin hemolyzed blood in the presence of meningitic fluid, although occasionally the hemolysis was delayed.

Brain tumor allowed no reading with the Bloor method, although a trace was present. In 2 cases saponin gave a partial or delayed hemolysis, also indicating a trace of cholesterol. In the other case no inhibition was present with saponin. One case of brain abscess gave a reading of 13 mgm. of cholesterol per 100 c.c. of fluid, but no inhibition of hemolysis took place. It may be interesting that the above case of brain abscess also had a meningitis which seemingly was terminal, as no meningeal symptoms were present throughout the disease. The cholesterol could not be due to the meningitis, however, as most cases of meningitis showed only a trace of cholesterol which could not be read in the colorimeter. Saponin caused hemolysis in the presence of the fluid from this case. The fluid from the other case of brain abscess was examined only for saponin hemolysis; hemolysis was delayed but not completely inhibited.

The 2 cases of hemorrhage of brain under observation both gave a large amount of cholesterol, the amount being 8 mgm. per 100 c.c. of fluid in one case and 17 mgm. in the other. In both cases there was complete inhibition of saponin hemolysis. The fluid in the latter case was removed from the ventricles of the brain and was yellowish in color. In the other case the fluid was removed by spinal puncture and was colorless.

Of the three ventricular fluids examined one was a hemorrhage of the brain, and, as mentioned above, gave a high cholesterol reading in the colorimeter (17 mgm.) and a complete inhibition of saponin hemolysis. The other ventricular fluid, which also gave a high cholesterol reading (103 mgm.) and complete inhibition of saponin hemolysis, was obtained from a premature infant with a marked hydrocephalus. The appearance of the ventricular fluid, the high cell count with the predominance of polymorphonuclear leukocytosis and a strong globulin reaction make the diagnosis of a meningitis certain, although the type of the meningitis could not be diagnosed, as no organism was isolated from the fluid. The great amount of cholesterol in the fluid makes one suspect the presence of a hemorrhage of the brain in the case.

The third ventricular fluid was obtained from a case of hydrocephalus and gave no reading in the colorimeter and no inhibition of saponin hemolysis. This last fluid shows that under normal conditions, *e. g.*, when there is no hemorrhage or meningitis, ventricular fluid contains no cholesterol.

Discussion.—In the older literature there is only an occasional reference to cholesterol in cerebrospinal fluid. Thus Schlossberger,[4] Zdarek,[5] Panzer[6] and Coriat[7] speak of the presence of cholesterol in hydrocephalus fluid. Of late four attempts have been made to study cholesterol in various types of cerebrospinal fluid systematically. Pighini[8] found cholesterol in a large percentage of fluids of general paresis (88 per cent.), of epilepsy (66 per cent.) and of dementia precox (43 per cent.). Hauptmann[9] found that saponin hemolysis is inhibited by cerebrospinal fluid from cases of brain and cord tumor (100 per cent.); hemorrhage of the brain (85.7 per cent.), tabes (83 per cent.), cerebrospinal lues (65 per cent.), multiple sclerosis (46 per cent.). He thought that the inhibition is due to the presence of cholesterol. Chaufford, Laroche and Grigant[10] and Weston[11] found small amounts of cholesterol even in normal fluid.

[4] Analyse von hydrocephalischen Flüssigkeiten, Arch. f. physiol. Heilk., 1851, x, 581.

[5] Ein Beitrag zur Kenntniss der Cerebrospinalflüssigkeit, Ztschr. f. physiol. Chemie, 1902, xxxv, 202.

[6] Zur Kenntniss der Cerebrospinalflüssigkeit, Wien. klin. Wchnschr., 1899, xii, 805.

[7] The Chemical Findings in the Cerebrospinal Fluid and Central Nervous System in Various Mental Diseases, Amer. Jour. Insanity, 1903–4, lx, 733.

[8] Loc. cit.

[9] Loc. cit.

[10] Le taux de la cholesterine dans de liquide cephalorachidien normal et pathologique, C. R. de Soc. de Biol., 1911, lxx, 146.

[11] Cholesterol Content of Cerebrospinal Fluid, Jour. Med. Research, 1915, xxxiii, 119.

Pighini determined cholesterol qualitatively by the Liebermann method, Hauptmann studied it by a serological method, while Chaufford, Laroche and Grigant and Weston determined it quantitatively.

The methods used by the above workers varied. Pighini used 25 c.c. of fluid and employed a tedious and complicated method. Chaufford, Laroche and Grigant unfortunately do not give the method they employed nor how much fluid they used. Weston worked with postmortem fluid in very large quantities, this method being open to criticism, on the ground that cerebrospinal fluid is known to undergo chemical and physicochemical changes post mortem.

Our results do not agree with those of Chaufford, Laroche and Grigant or with those of Weston, in that we found no cholesterol at all in normal fluids. Nor do our results coincide with those of Pighini, who found cholesterol in a very large percentage of fluids with a positive Wassermann reaction.

Our cases of brain tumor have been too few in number to express an opinion as to the accuracy of Hauptmann's statement. With the Bloor method there was only a trace of cholesterol in the two cases of brain tumor in which this method was used, and with the saponin method there was partial inhibition. The one case of brain abscess examined quantitatively gave a high reading of cholesterol in the colorimeter. There was, however, no distinct inhibition of saponin hemolysis, nor was there marked inhibition in the fluid from brain abscess examined only qualitatively.

Our results in hemorrhage of the brain agree with those of Hauptmann, there being a large amount of cholesterol with the Bloor method and complete inhibition of saponin hemolysis.

With minor exceptions the saponin method of Hauptmann agreed fairly well with the Bloor method, although the latter is more quantitative and more sensitive. This also shows that Hauptmann was right in his contention that the inhibition of hemolysis in some fluids is due to cholesterol.

The above results, we believe, show that the amount of cholesterol in pathologic cerebrospinal fluid depends wholly or in part on the degree of permeability of the meninges and has no specific pathogenesis. This is evident by the presence of a trace of cholesterol in all cases of meningitis and by the presence of large amounts in hemorrhage of the brain. It is also evident from our work that the claim of Pighini of the dependence of a positive Wassermann reaction on cholesterol has no foundation.

The usefulness of the cholesterol determination in cerebrospinal fluid for diagnostic purposes, we believe, is limited because of its presence in hemorrhage of the brain, in some cases of meningitis and also occasionally in general paresis. Still, its presence is corroborative evidence of the existence of a pathologic process producing increased permeability of the meninges. Whenever the

history of the case indicates it, hemorrhage of the brain should therefore be thought of, especially when large amounts of cholesterol are present.

Conclusions.—Normal cerebrospinal fluid contains no cholesterol or only a very small trace of cholesterol.

Fluid in which the Wassermann and Lange reactions are positive contains no cholesterol in appreciable amounts. Only three out of twenty-five such fluids gave a reading in the colorimeter.

Fluid of hemorrhage of the brain showed high cholesterol content.

Fluid from tumor of the brain gave a trace of cholesterol.

Fluid from a case of brain abscess gave a high cholesterol reading.

The majority of meningitis fluids showed a trace of cholesterol. Three fluids had a high reading.

Ventricular fluid gave no cholesterol reading, except when there was the presence of hemorrhage of the brain or other pathologic condition.

The Hauptmann reaction seems to depend on the cholesterol content of the cerebrospinal fluid.

This work does not bear out Pighini's contention that the Wassermann reaction depends on the cholesterol of the fluid.

We believe that the cholesterol content depends wholly or partially on the permeability of the meninges.

CASES IN WHICH CHOLESTEROL WAS FOUND IN APPRECIABLE AMOUNTS BY THE BLOOR METHOD.

Name.	Diagnosis.	Quantity of fluid used.	Wassermann.	Cholesterol (Bloor) mgm. per 100 c.c.	Saponin.	Remarks.
P. P.	General paresis	6.0 c.c.	++++	13.3	Complete hemolysis	
Mixture	General paresis	10.0 c.c.	++++	6.2	Delayed hemolysis	
E. C.	Pneumococcus meningitis	3.0 c.c.	Negative	19.0	Inhibition in waterbath; hemolysis in twelve hours	Fluid drawn while patient was moribund.
M. N.	Tuberculous meningitis	5.0 c.c.	Negative	10.2		
S. S.	Meningitis	2.3 c.c.	++++	14.1	.....	Type of meningitis undetermined.
L. P.	Cerebral hemorrhage	3.0 c.c.	Negative	8.0	Partial inhibition	
B. A.	Meningeal hemorrhage; meningitis	3.0 c.c.	Negative	17.0	Inhibition	Ventricular fluid.
B. S.	Hydrocephalus; meningitis; meningeal hemorrhage ?	3.0 c.c.	Negative	103.0	Complete inhibition	Ventricular fluid.
J. C.	Brain abscess; terminal meningitis	6.0 c.c.	Negative	13.0	Complete hemolysis	Native amboceptor present.

PULSE-RATE AND BLOOD-PRESSURE RESPONSES OF MEN TO PASSIVE POSTURAL CHANGES.*

By Max M. Ellis.

(From the Medical Research Laboratory of the Air Service, Mitchel Field, Long Island, N. Y.)

The development of the airplane has added interest to the circulatory response of men following passive alterations of body position, for the aviator is subjected frequently to sudden variations in body position, which are largely passive as far as his musculature is concerned. Changes in pulse-rate and blood-pressure correlated with changes in body position made by the subject, have been studied by many investigators, but the changes in circulation accompanying postural changes in which the subject is moved by some force outside of his body, have not received the same attention.

In experiments on animals Hill ('95) showed that the blood-pressure in the carotid artery was increased by tilting the animal from the horizontal to the head-down position and decreased by tilting from the horizontal to the head-up position. Barach and Marks ('13), working with young men fifteen to thirty years of age, on a tilting table, concluded that "when the element of muscular effort has been eliminated, change of body posture from the erect to the horizontal will cause an increase in the maximum pressure, a decrease in the minimum pressure and an increase in the pulse-pressure." Henderson and Haggard ('18) followed the circulatory responses in the head-down position of ten young men on the tilting board, and report that "in the inverted or head-down position (30 to 45 degrees) the heart-rate in ten men was slower than in the flat position by an average of 9.5 beats a minute and slower than the erect position by 17." Excepting two cases (in the tilt from the erect to the reclining position) all of the pulse responses were minus in the tilts which lowered the head and plus in those which raised the head. The responses in systolic and diastolic pressures were not so uniform. The systolic pressure of five of the ten men and the diastolic pressures of all ten fell on changing from the erect to the horizontal. On tilting from the horizontal to the head-down position the systolic pressure rose in some cases and fell in others, the subjects being about equally

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divided between the two responses. The same was true of the responses to the return tilt, *i. e.*, from the head-down position to the horizontal. The diastolic responses following both of these tilts were also about equally divided between plus and minus. Although the work of Stephens ('04) is not strictly comparable with the preceding articles because his subjects were not tilted except from the reclining to the head-down position, his averages of the responses in pulse-rate, and systolic-pressure to changes in body position are interesting in this connection. These averages show a decrease in the per minute heart-rate and an increase in the systolic blood-pressure from the erect position, through the sitting and reclining positions to the head-down position. Stephen's data were collected after the circulatory balance was reached by his subjects. More recently Barach ('19) summarizes the responses in pulse-rate, systolic and diastolic pressure of 48 normal adults to two passive tilts. When these subjects were tilted from the standing position to the reclining he found that the pulse-rate and diastolic pressure fell and the systolic pressure rose. Following the return tilt from reclining to standing position the pulse-rate and diastolic pressure rose and the systolic pressure fell.

These observations collectively suggest that the circulatory responses of men to passive tilts which lower the head are a decrease in the per minute pulse-rate, an increase in the systolic pressure (sometimes a decrease) and a decrease in the diastolic pressure (sometimes an increase).

The present study was undertaken at the Medical Research Laboratory of the Air Service with a view to obtaining additional data on the constancy of these responses of men to passive postural changes of various sorts and on the degree of these responses.

Fifty young men, twenty to thirty-one years of age, drawn from the medical department and from the air service of the army, were used as subjects. Each man was given the routine physical examination by an internist and by an ear, nose and throat specialist before selection for these tilt tests. No man not reported sound was taken. All of the subjects were familiarized with the tilting table and its operation before the tests were made, to eliminate the factor of surprise. During the tests the subject refrained from talking and the observers spoke only when necessary.

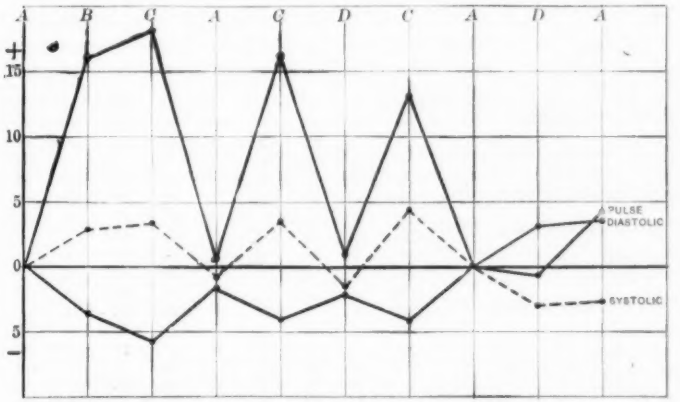
The tilting tests were made by two observers, one taking the pulse counts and the other the blood-pressures throughout the test. The subject was placed on the tilting table and swung up into the horizontal plane, here termed the reclining position, after the blood-pressure apparatus was attached to the left arm (a Tycos apparatus was used and the readings taken by auscultation) the subject was undisturbed ten minutes, when the first records of pulse and blood-pressure were taken simultaneously. Three readings were made and the averages taken as the normals against

which the subsequent readings in other positions were checked. As soon as the normals were established the subject was tilted quickly and quietly into the new position and a new reading taken. As assistants were always present to look after the mechanical side of the tilting the observers were able to make the first count of pulse-rate and the first measurements of blood-pressure within thirty seconds after the tilt. These figures have been recorded in the tables as the "immediate response." After the immediate response was recorded the subject was again undisturbed for five minutes. At the end of five minutes a second set of records were taken which have been termed the "response at the end of the fifth minute." These readings completed, the subject was tilted to the next position and the process repeated. Effort was made to take all readings at the end of expiration, but this was not always possible. From these several sets of readings the amount and direction of change in the pulse-rate and blood-pressures during the first thirty seconds after the body position was altered the amount and direction of change at the end of the fifth minute and the amount and direction of change during the five minutes in each position were obtained. In establishing these values the readings in a given position were compared with those taken at the end of the fifth minute in the preceding position. Five minute intervals were chosen because it was found by preliminary tests in which minute to minute readings were taken, that the subjects generally reached their maximum responses and adjustments to the new position within the first three minutes after the tilt was made.

Two series of tilts were used. In the first series the subject was tilted from the reclining position to head up 45 degrees, head up 45 degrees to standing, standing to reclining, reclining to standing, standing to head down 45 degrees, head down 45 degrees to standing. In the second series the first three changes of position were identical with the first three of the first series, *i. e.*, from reclining through head up 45 degrees and standing to reclining again. Then followed tilts from reclining to head down 45 degrees and head down 45 degrees to reclining (see Chart).

General Responses. Considering the responses in pulse-rate, systolic pressure and diastolic pressure separately, correlated only with the changes in the position of the subjects, the responses in pulse-rate were the most uniform of the three. Ninety per cent. of all cases in which the head was elevated during the tilt showed an immediate rise in pulse-rate and 84 per cent. had a higher pulse-rate at the end of the fifth minute after a tilt which elevated the head than at the end of the fifth minute in the previous position. The opposite tilts, those in which the head was lowered, gave much the same grouping of cases, with the opposite pulse response. Ninety-one per cent. showed an immediate fall in

pulse-rate on lowering the head and 86 per cent. had a lower pulse-rate at the end of the fifth minute than in the previous position. The predominant pulse responses, therefore, to all changes of position taken collectively were (1) an increase in pulse-rate—plus response—on raising the head, and (2) a decrease in pulse-rate—minus response—on lowering the head. All of the several types of tilts produced these responses, as from 62 to 100 per cent. of the cases in each tilt gave the responses designated above as the predominant responses. In the main these predominant responses were supported by larger percentages immediately after the tilt was made than at the end of the fifth minute, suggesting that the pulse response was compensatory to the sudden change



Average deviations in pulse-rate, systolic pressure and diastolic pressure from the reclining normals at the end of the fifth minute after each tilt. Tilts plotted in sequence used in the tests. Pulse-rate plotted in beats per minute and blood-pressures in millimeters of mercury: *A*, reclining; *B*, head up 45 degrees; *C*, standing; *D*, head down 45 degrees.

in position of a considerable volume of blood by gravity, and that additional responses during the next five minutes completed the adjustments to the new body position. This is confirmed by the changes in blood-pressure during the five-minute interval. In some of the tilts these readjustments amounted to a change in the character of the blood-pressure response from minus to plus. Although in other tilts this shifting of blood-pressure was not so profound, in all tilts excepting that from head down to standing more of the subjects showed a zero blood-pressure response at the end of the fifth minute than immediately after the change of position (Table I).

The blood-pressure responses were not so sharply grouped as were the pulse-rate changes. The predominant responses in

general, as indicated by the highest percentages, were a fall in systolic pressure and a rise in diastolic pressure following those tilts which raised the head; and a rise in the systolic pressure and a fall in the diastolic pressure following those tilts which lowered the head. The diastolic pressure varied in the same direction as the pulse-rate and the systolic pressure in the opposite direction. The predominant blood-pressure responses were supported by much smaller percentages than were the changes in pulse-rate. In several of the tilts the cases were about equally divided between plus and minus blood-pressure responses, indicating that the blood-pressure responses were much less constant than the pulse-rate changes.

TABLE I.—RESPONSES TO TILTS.

Tilt.	Cases.	Pulse.			Systolic.			Diastolic.		
		Rose.	Held.	Fell.	Rose.	Held.	Fell.	Rose.	Held.	Fell.
All tilts raising head .	244	**90**	5	5	17	9	**74**	**58**	7	35
		84	5	11	21	21	**58**	**60**	20	20
All tilts lowering head	108	8	1	**91**	**48**	9	43	18	8	**74**
		6	8	**86**	**48**	13	39	24	9	**67**
Head down to reclining	46	**79**	4	17	38	22	38	34	22	**44**
		69	14	17	38	18	**44**	**47**	23	30
Head down to standing	32	**100**	0	0	33	0	**67**	**67**	0	33
		100	0	0	17	17	**67**	**83**	0	17
Reclining to head up 45 degrees . . .	58	**100**	0	0	4	4	**92**	**82**	4	14
		100	0	0	18	14	**68**	**76**	10	14
Reclining to standing	50	**100**	0	0	12	8	**80**	**68**	4	28
		100	0	0	20	24	**66**	**68**	24	8
Head up 45 degrees to standing . . .	58	**79**	17	4	14	7	**79**	41	4	**55**
		62	7	31	18	27	**55**	**41**	24	35
Reclining to head down 45 degrees . . .	34	17	0	**83**	12	12	**76**	36	12	**52**
		12	17	**71**	24	12	**64**	**59**	17	24
Standing to reclining	42	5	0	**95**	**76**	0	24	14	5	**81**
		5	5	**90**	**71**	5	29	19	5	**76**
Standing to head down 45 degrees . . .	32	0	6	**94**	**50**	19	31	19	0	**81**
		0	0	**100**	**50**	25	25	19	6	**75**

Data given in percentages for direct comparison. First line in each pair gives the immediate response as compared with the normal in the previous position; the second line gives the response at the end of the fifth minute after the tilt.

Three separate tilts did not follow the predominant responses of blood-pressure as determined by the mass data of all classes. In the reclining to head-down tilt the systolic responses of 76 per cent. of the cases were minus immediately after the tilt, and 64 per cent. held a systolic pressure lower than the reclining normal to the end of the fifth minute. The diastolic pressures of 52 per cent. also fell below the reclining value immediately after the tilt (the response expected from the predominant responses of the mass data of head lowered tilts), but in 59 per cent. of the cases of this tilt the diastolic pressure rose during the five-minute interval above the reclining normal. In the reclining to head-down tilt, therefore,

the pulse response followed the typical response of all head-down tilts, the systolic pressure fell instead of rising and the diastolic pressure fell as expected immediately after the tilt but rose above the reclining value during the next five minutes. The other two exceptions to the predominant responses of the mass data were in the diastolic pressure responses. In both the head down to reclining and head up 45 degrees to standing tilts the immediate diastolic response was a fall in pressure below the former value, followed by a rise during the next five minutes. The diastolic exceptions in all three tilts, therefore, were all of one type, an initial fall regardless of the position from which the tilt was made, followed by a rise above the value in the preceding position during the next five minutes. It is to be noted also in this connection that in each of the three tilts in which the diastolic pressure did not follow the predominant response of the mass data the cases of each tilt were about evenly divided between plus and minus response. As is shown under the discussion of the degree of change in these three tilts the actual amount of change in pressure measured in millimeters of mercury was slight and the diastolic pressures in these three tilts may represent indifferent responses.

If the predominant responses in pulse-rate, systolic pressure and diastolic pressure, as determined in Table I by the largest percentage of cases in each tilt group, be summarized in a formula (P = pulse, S = systolic pressure, D = diastolic pressure), $P + S - D +$ represents the predominant responses of the largest percentage of cases to a passive tilt in which the head was raised, regardless of the initial position from which the tilt was made. Similarly, $P - S + D -$ represents the predominant responses of cases in which the head was lowered, excepting the tilt from reclining to head down. In this tilt the largest percentage of cases gave the $P - S - D +$ responses.

These three formulæ of responses from the mass data were applied to the actual records of each individual case to determine the degree of correlation existing between the three responses of pulse-rate and systolic and diastolic pressures. The responses at the end of the fifth minute after the tilt were used (Table II). Only one-third of all cases in which the head was elevated during the tilt gave the expected responses in all three variables, pulse-rate, systolic and diastolic pressures. In the tilts lowering the head the percentage was slightly higher but still below 50 per cent. In only two tilts did the percentages of cases agreeing with the formula of responses exceed 50 per cent. in the head down to standing tilt and in the reclining to head up 45 degrees tilt. Cases giving any two of the predicted responses were more numerous, including 50 per cent. or more of the subjects in each tilt with the exception of the head down to reclining tilt. A comparison of the cases giving any two of the expected responses suggests there is little difference

in the constancy of the systolic and diastolic blood-pressures, as the *P S* and *P D* groups were about the same. Fewer subjects gave both of the predicted blood-pressure responses than gave the predicted pulse and either one of the blood-pressure responses. This was excepted from the summary of the mass data (Table I) as the pulse-rate changes were the most constant of the three responses. This confirmation of the grouping in Table I gives added value to those percentages, which show not only the relative constancy of each response but also that the predominant method of compensation was a change in pulse-rate.

It is evident from Table II that the responses to changes in position were not equal in the three variables, pulse-rate, systolic pressure and diastolic pressure, and that there was no stereotyped response which included the majority of cases. Satisfactory compensations, at least such as would maintain the individual for five minutes without loss of consciousness (none of the subjects fainted during the tilts) were made by other combinations of pulse, systolic and diastolic responses than those expected from the mass data.

TABLE II.—CORRELATIONS OF THE THREE RESPONSES, PULSE-RATE (P), SYSTOLIC PRESSURE (S) AND DIASTOLIC PRESSURE (D). DATA IN PER CENT. OF CASES GIVING RESPONSES INDICATED.

Tilt.	P+S−D+ Per cent.	P−S− Per cent.	P+D+ Per cent.	S−D+ Per cent.
Head down to reclining	13	30	39	26
Head down to standing	67	67	83	67
Reclining to head up 45 degrees	55	72	70	55
Reclining to standing	32	50	56	32
Head up 45 degrees to standing	21	48	27	30
All head up cases	33	52	50	38
	P−S+D− Per cent.	P−S+ Per cent.	P−D− Per cent.	S+D− Per cent.
Standing to head down	31	50	70	31
Standing to reclining	38	57	62	43
	P−S−D+ Per cent.	P−S− Per cent.	P−D+ Per cent.	S−D+ Per cent.
Reclining to head down	47	58	53	47

Degree of Response. In Fig. 1 the mean values of change in pulse-rate per minute and blood-pressure in millimeters of mercury have been plotted, taking the several tilts in the sequence in which they were made on the subject. The mean values were obtained after the actual values of all individual cases had been plotted by classes. As the pulse-rate counts were made in twenty-second units and multiplied by three a deviation of plus or minus one count by the observer has been allowed, and similarly a deviation of

plus or minus one unit (2 mm.) on the Tycos dial has been allowed in the blood-pressure readings. The zero class of the pulse values included, therefore, all cases whose responses varied from plus three beats to minus three beats per minute and the zero classes in the blood-pressure all from minus 2 mm. to plus 2 mm. The class ranges for pulse-rates were nine beats per minute and for blood-pressure 6 mm. of mercury.

The tilts from reclining to head up 45 degrees and from reclining to standing gave almost identical degree changes, being P +16 beats, S −3.5 mm., D +3 mm. and P +16, S − 4, D +3.5 respectively at the end of the fifth minute after the tilt. When the standing position was reached by two tilts, *i. e.*, reclining to head up 45 degrees and head up 45 degrees to standing, greater deviations from the reclining normals of pulse-rate, systolic and diastolic pressures were obtained, the responses at the end of the fifth minute of standing after these two tilts being, P +18, S −5.5, D +3.5. These values equal or exceed each of the three responses to either the reclining to head up 45 degrees tilt or the reclining to standing tilt. When the standing position was reached by one tilt from the head-down position, *i. e.*, the head down to standing tilt the pulse response was smaller and the diastolic response greater than either of the other two standing values. The response at the end of the fifth minute of standing after the head down to standing tilt were P +12, S −2, D +6 and the deviations from the reclining normals P +13, S −4, D +4.5.

In the reverse tilts, standing to reclining, opposite responses obtained, P −17.5, S +4, D −4, so that the readings at the end of the fifth minute in the reclining position were almost identical with the normals taken in the reclining position. In the standing to head-down tilt the response in pulse was not as great as in the standing to reclining tilt being P −15, S +2, D −5. Although less than the responses from standing to reclining these values following the standing to head-down tilt are fairly close reverse responses to those following the head down to standing tilt. The responses after that tilt were P +12, S −4, D +4.5. It is evident that a subject does not relax as completely in the unusual position of head down 45 degrees as in the reclining position, and the factor of muscular effort, either conscious or unconscious, is not completely eliminated in the head-down position. Similarly a certain amount of muscular effort on the part of the subject cannot be avoided in the standing position even though the subject is brought to this position by forces outside of his body. In the head down to standing tilt, therefore, the muscular effort of the subject and the movement of the blood by gravity both contributed to the reactions of the subject.

In order to ascertain the responses to the head-down position following a tilt from a position in which the muscular effort of the

subject was eliminated as far as possible, part of the subjects were tilted from the reclining to the head-down position and then back to the reclining position. The responses at the end of the fifth minute in the head-down position following the reclining to head-down tilt were quite different from those at the end of the fifth minute in the head-down position following the standing to head-down tilt. Following the reclining to head-down tilt the deviations from the reclining normals were P -0.5, S -4, D $+3$ at the end of the fifth minute as compared with P $+1$, S -2.5, $D-1.5$ at the end of the fifth minute after the standing to head-down tilt. After the return tilt, head-down to reclining, the subjects did not return to the reclining normals in five minutes, the average deviations from the reclining normals being P $+4$, S -2.5, D $+3.5$.

From these various degree values it seems that the subjects examined made rather complete adjustments in five minutes to tilts in the reclining-standing quadrant, as the changes in pulse and blood-pressure in one direction are offset by approximately equal changes in the opposite direction on reversing the tilt. In the reclining to head-down quadrant the responses were much less uniform, and the circulatory balance was probably not established in the five-minute interval. Tilts starting in the reclining-standing quadrant and ending in the reclining-head-down quadrant, or *vice versa*, gave more uniform and also more profound responses than tilts in the reclining-head-down quadrant alone. These tilts, however, which carried the subject through more than 90 degrees, showed the disturbing effect of the head-down position, either at the beginning or the end of the tilt, upon the general compensations of the body to changes in position.

Considering the mass data of all cases collectively the responses obtained from these fifty men were in general the responses expected from the review of previous experimentation. The formulæ $P+$ $S-$ $D+$ for the tilts raising the head and $P-$ $S+$ $D-$ for those lowering the head, included the largest percentages of responses in all tilts excepting the reclining to head-down tilt, the mass responses of which were $P-$ $S-$ $D+$. The application of these formulæ, however, to the individual cases showed that a relatively low percentage of the individuals actually gave these three responses simultaneously and that these formulæ were therefore unreliable for the study of individual subjects even among men who had been pronounced in good physical condition. The response to passive changes in body position, as evidenced by the data here offered, was primarily one of change in pulse-rate. The blood-pressure responses were much more subject to individual variation in the general adjustment following these passive body position changes, although the blood-pressure responses did show definite groupings in the mass data. As the effect of the shifting

suddenly of a quantity of blood by gravity could produce through its effect on the nervous mechanism controlling the heart, changes in pulse-rate such as followed the changes in body position, and as several other factors are involved in the blood-pressure changes, a greater constancy of the pulse responses might be expected.

The responses in systolic pressure to the reclining to standing tilt were so different from those given by Crampton ('13), for healthy men on standing from the reclining position that the mass data may be reviewed here for comparison. Crampton states "that in the perfectly normal there occurs upon rising from the recumbent position a vasoconstriction effort which squeezes these veins (splanchnic) and raises the blood-pressure, which more than overcomes the hydrostatic load." In the tilt from reclining to standing the mass response was a fall in systolic pressure, supported by 80 per cent. of the cases immediately after the tilt, and by 66 per cent. at the end of the fifth minute, instead of the rise in systolic pressure found by Crampton in the men who stood voluntarily. As the subjects used in these tilting tests had been reported sound by the examining surgeons the vasomotor tone of the subjects was presumably good. The fall in systolic pressure following the tilting of these men from reclining to standing suggests either a lag in this compensatory vasoconstriction effort or a greater demand for compensation than could be met by the splanchnic area alone. As the percentage of cases giving the fall in systolic pressure fell during the five-minute interval from 80 to 66 per cent. there was some compensation which raised the blood-pressure during the five-minute period in at least 14 per cent. of the cases. In the case of the individuals rising by their own muscular efforts the tightening of various muscles of the body which would occur in the act of rising, would in part prevent the fall in pressure which took place in the reclining subjects who were suddenly tilted into the standing position. The relative demand, therefore, for compensation from the splanchnic vessels would be greater in the case of the tilted subjects than in that of the subjects rising by their own muscular effort.

Summary. 1. In general tilts elevating the head gave a rise in pulse-rate, a fall in systolic pressure and a rise in diastolic pressure, and those lowering the head a fall in pulse-rate, a rise in systolic pressure and a fall in diastolic pressure. The conspicuous exception to these responses was the reclining to head-down tilt in which the largest percentage of cases gave a fall in pulse-rate, a fall in systolic pressure and a rise in diastolic pressure.

2. The individual data showed that only a little over one-third of all cases gave the three responses in pulse-rate, systolic and diastolic pressures expected from the mass data, simultaneously.

3. Tilts from reclining to head down 45 degrees and return gave the least constant responses of all the tilts used.

4. The tilt from reclining to head up 45 degrees produced almost the same degree of responses as the tilt from reclining to standing.

5. With the exception of the tilts in the head down to reclining quadrant the responses given to any tilt were offset by approximately equal opposite responses when the tilt was reversed.

6. The initial and final positions of the subject had more effect on the degree of responses following a tilt than did the distance travelled by the subject during the tilt.

The writer wishes to acknowledge his obligations to Lieut. Harry Fried, M.C., who assisted in a large number of these tilting tests.

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LABORATORY AIDS IN THE DIAGNOSIS OF GONOCOCCAL INFECTIONS, WITH SPECIAL REFERENCE TO THE GONOCOCCUS COMPLEMENT-FIXATION TEST.

By Robert A. Kilduffe, A.M., M.D.,

DIRECTOR OF LABORATORIES, PITTSBURGH HOSPITAL; DIRECTOR OF LABORATORIES, MCKEESPORT HOSPITAL; BACTERIOLOGIST TO THE CITY OF McKEESPORT; SEROLOGIST, PROVIDENCE HOSPITAL; FORMERLY MAJOR, M.C., U.S.A.

(From the Laboratories of the Pittsburgh Hospital.)

The present intensive campaign for the education of the general public in regard to the incidence, treatment and prevention of venereal diseases will, it is hoped, do much to lead to their early recognition, and, following upon this, and instructions as to their infectivity—which must, of necessity, form part of their treatment—great strides in their prevention are to be hoped for.

Indeed, it is now not an infrequent occurrence for those about to marry to seek information as to their freedom from venereal infection and because of this fact, and because, particularly in cases of long standing or those whose infection long antedates their visit to the doctor, the question as to their ability to infect others is a matter difficult to decide, a *resume* of the laboratory aids in the diagnosis of gonococcal infections seems timely.

In spite of the fact that the recognition of the typical case of gonorrhea is, as a rule, a matter of no difficulty, there are a number of cases of urethritis, especially in the female, where the diagnosis is not readily to be made.

A wrong positive diagnosis is an injury to the patient not readily

repaired; a wrong negative diagnosis may cause irreparable harm to the patient, his family and to the community, and every method available to avoid either error should be called upon whenever possible.

It is, of course, an obvious and admitted fact that not all cases can be recognized with absolute certainty by laboratory methods alone. There is always the latent case, the chronic case, especially in the female, in which bacteriologic evidence as to its origin is lacking; and in such cases, as in other conditions, the clinical evidence must be the deciding factor. However, in a certain number of cases specific evidence can be elicited if the proper methods are applied, and to call attention to these is the object of this paper. As always, it must be remembered that it is not the test but its interpretation which is of value.

Cases in which laboratory evidence of gonococcal infection is to be sought for may be divided into three groups: (*a*) Acute infections actually or suspected to be of gonorrheal origin; (*b*) cases in a chronic stage either with or without a history of previous acute infection; (*c*) cases which may be looked upon as presenting secondary manifestations of the disease, examples of which are arthritis in the male and salpingitis in the female.

Bacteriologic Diagnosis of Acute Infections. These may be accompanied by a history of diagnostic value, or this may be entirely lacking, as is usually the case in the female. In the male, as a rule, the presence of an acute, urethral discharge is preponderating evidence of gonorrhea; because, however, of the occasional case of non-specific urethritis, an error in the diagnosis of which may lead to dire results, a microscopic examination of the stained smear is indicated.

There are several points in the preparation of such specimens, minor details in themselves, perhaps, but all, in their summation, enhancing or vitiating the value of the examination.

1. The patient should not void for at least an hour previous to taking the specimen, thus avoiding flushing out of the canal.

2. The smear should be from the urethra. This is of particular importance in the female, for nothing is of less diagnostic value, except in the vulvovaginitis of children, than a hastily taken smear from the vagina. In the adult female additional preparations should be made from the cervix and so labelled.

3. The smear should not be too thick, as the difference between Gram-negative and Gram-positive organisms may be a matter of some difficulty to determine, because the thickness of the smears protects them from the action of the reagents.

4. The smears should be taken in duplicate upon microscopic slides or cover-glasses which should be allowed to dry spontaneously before being placed in contact. Nothing is more unsatisfactory than slides which have been placed together while moist, have adhered upon drying and must be pried apart for staining.

5. Douches, injections, washes and the like should not be used just prior to taking the specimens.

While the typical gonococcus is readily recognized by those familiar with its morphology, in the simple, single-stained preparation, such as Loeffler's methylene blue, the fact that many times they may not be typical in appearance and that there are other organisms which morphologically resemble them in appearance, renders the use of Gram's staining technic advisable as a routine.

Chief among the organisms morphologically resembling the gonococcus is the meningococcus, which, however, is not often found in the same localities; other organisms of more importance as being seen in urethral smears are coccoid forms of the colon bacillus, phagocytized cocci which, as a result, may stain indifferently, and the Micrococcus catarrhalis.

What are the criteria for the recognition of the gonococcus in the stained smear? It must be Gram-negative; it must be a diplococcus and typical bean- or kidney-shaped forms must be demonstrated in some area of the smear, and careful search should demonstrate some intracellular forms. In this connection it must be borne in mind that, in the acute discharges, the majority of the gonococci are not infrequently entirely extracellular.

These conditions, having been fulfilled in the presence of an acute discharge with or without a suspicious clinical history, suffice to render the diagnosis of gonorrheal infection justifiable.

The exact technic of Gram-staining deserves a word of mention, as it is the rock on which many stumble. There are several sources of error inherent in the method itself if minor details are not carefully attended to.

1. The gentian-violet solution made with anilin water must be relatively fresh, and even when other solutions of more stable character, such as Stirling's stain, are made use of the stain should be frequently tested with known Gram-positive organisms.

2. The film must not be too thick, as decolorization may be difficult and unsatisfactory.

3. The films should be allowed to dry spontaneously, and care should be taken to avoid overheating when fixing, as atypic staining may occur.

4. The iodin solution should be stronger than that in the original formula, the water being reduced from 300 c.c. to 100 c.c. (iodin, 1 gram; potassium iodide, 2 grams; distilled water, 100 c.c.).

5. The alcohol used for decolorizing should not be weaker than 95 per cent. to absolute and should not be allowed to act for too long a time, as Gram-positive organisms resist its action only for a reasonable period and exposure of the film to alcohol for longer than two or three minutes will give confusing results.[1]

[1] M. W. Lyon (Jour. Am. Med. Assn., October 9, 1920, No. 15, lxxv, 1017) has recently advocated the use of acetone as a decolorizing agent for the Gram stain, applying it instead of alcohol for five to ten seconds. Some experience with the method would seem to bear out the claims made for it.

6. The counterstain must be in watery solution, must not be too strong nor allowed to act for too long a time, as it may, in such case, replace the gentian-violet and give false Gram-negative pictures.

A satisfactory technic follows. As a preliminary it is well at frequent and definite intervals, to test the stain and the technic with a known Gram-positive organism, such as the Staphylococcus aureus and a known Gram-negative organism, such as Bacillus coli, both of which are readily obtained.

Technic for Gram-staining. 1. Fix the dried film by passage through the flame, testing the degree of heat on the hand.

2. Cover with gentian-violet solution for one minute.

3. Wash off the gentian-violet solution with Gram's iodin solution (amended formula) and replace with another fresh portion of iodin solution, which is allowed to act for one minute.

4. Wash off the iodin solution with alcohol (95 per cent. to absolute), not with water, and flood the film with alcohol, tilting the slide to allow the alcohol to flow back and forth until no more violet color is given off. The action of the alcohol should not be prolonged for more than two or three minutes, which will be sufficient if the film is of the proper thickness.

5. Counterstain thirty seconds with a weak, watery solution of Bismarck brown, eosin (0.5 per cent.) or a very dilute solution of carbol-fuchsin (two drops to a test-tube full of water).

6. Wash in water, blot and mount.

It must be remembered, in the interpretation of the stained smear, that the fact that an organism is Gram-negative, and intracellular does not, therefore, determine it as a gonococcus; familiarity with the variations in its morphology are essential. As in all other laboratory examinations, in the final analysis the value of the procedure is in direct proportion to the degree with which it is correlated with the clinical findings; in a word, it is the interpretation which counts.

Summing up: For the identification of the gonococcus in the stained smear, the following conditions must be fulfilled: (*a*) The smear must be properly and intelligently taken and must not be too thick; (*b*) the staining technic must be properly controlled; (*c*) the observer must be familiar with the microscopic appearance of the gonococcus and allied organisms and thoroughly capable of interpreting what he sees in terms of its relations to the patient.

These premises being fulfilled and the findings correlated with the clinical evidence the bacteriologic diagnosis of acute gonorrheal infections may be made with a fair degree of certitude.

In the comparatively infrequent cases of gonococcus bacteremia cultures are required, the preparation and study of which require a trained bacteriologist, so that they are merely mentioned here.

Bacteriologic Diagnosis of Chronic Infections. It is in cases of this group—those in which the history of a previous acute attack is not infrequently wanting and in which the clinical evidence is not

always sufficiently clear to permit of a definite diagnosis—that the laboratory is most frequently called upon to make a decision.

Here, also, we may place those individuals who, admitting a previous infection, but being without symptoms, are desirous of obtaining evidence as to their freedom from foci which might prove a source of infection to others.

We may adopt any or all of three procedures: (*a*) Microscopic examination of stained films from selected areas; (*b*) the production of an acute discharge in which gonococci may be found or the production of an acute, focal reaction; or (*c*) the use of the gonococcus complement-fixation test.

The efficacy of the first of these depends entirely upon the locality from which and the method by which the film is taken, for, in the majority of cases, the success or failure of the examination as to decisiveness will stand or fall upon the character of the film examined.

It is necessary to keep in mind the lurking places of the gonococcus and to remember that it may be present in these places without the coincident presence of any discharge. In the male these localities are: (*a*) The follicles of the urethra; (*b*) Cowper's glands opening into the bulbous portion of the urethra; (*c*) the prostate; (*d*) the seminal vesicles; (*e*) rarely in the bladder.

It is necessary, therefore, for films to be made and examined from the following: (1) Material expressed by milking the urethra; (2) material obtained by the introduction of a sterile swab into the urethra; (3) from the material obtained by prostatic massage; and (4) from the centrifugalized sediment of an ounce or so of urine passed at the time of the examination.

In the female the gonococcus may persist in: (1) The urethra and the urethral ducts; (2) Bartholin's glands; (3) the cervix; (4) the uterus and Fallopian tubes.

Smears must therefore be made from material secured by milking the urethra or the introduction of a sterile swab, from material expressed from Bartholin's glands, secretion from the cervix, or, rarely, from the uterine cavity.

It must be remembered that even these procedures may fail, for the gonococcus may still be present in other localities than those examined, as in the Fallopian tubes, or, when present, may be buried in the deeper cell layers and not liberated at the time of examination. Under these circumstances an attempt may be made to produce a focal reaction by the administration of gonococcus vaccine, which may be manifested by the production of an acute discharge containing the gonococcus or by pain and tenderness in areas of metastatic gonococcal infection. Acute discharges may be produced by the use of irritants, such as silver nitrate solution.

Several observers, notably Irons,[2] Bruck,[3] and Reiter,[4] have

[2] Jour. Infect. Dis., 1908, v, 279.
[3] Deutsch. med. Wchnschr., 1909, xxxii, 470.
[4] Ztschr. f. Geburtsh. u. Kinderh., 1911, lviii. 571.

reported upon the occurrence of focal reactions following the use of vaccines, but there is an element of danger in the procedure in that a latent infection may be converted into an acute one not readily controlled.

It may be noted in passing that Irons[5] has reported upon the production of cutaneous reactions, similar to those obtained in the von Pirquet test, occurring with gonococcal extracts; but as the cutaneous sensibility of various individuals seems to vary, and, indeed, the same individual may show extreme variations—possibly due to varying amounts of bacterial protein in the extracts used—the test is limited in value and not generally used.

The Gonococcus Complement-fixation Test. Depending, as does the Wassermann, upon the absorption or fixation of complement, the gonococcus complement-fixation test differs from it in being a true biologic reaction in that the antigen is a true antigen composed of suspensions or extracts of the causative organism.

Müller and Oppenheim[6] were the first to report the occurrence of the reaction, further reports later emanating from Bruck[7] and Meakins,[8] who published the first American report in 1907. The work of Teague and Torrey,[9] Torrey,[10] Wollstein,[11] Watabiki,[12] Harrison,[13] Ower,[14] and particularly that of Schwartz and Schwartz and McNeilk,[15 16 17] was largely instrumental in placing the test on a practical basis, and numerous reports have now been made upon its specificity and value in determining absolute cure.

Particular advantages of this method of testing for the presence of gonococcal infection are the fact that the specimen is easily taken and the patient is not thereby informed as to the nature of the examination.

It is not, however, as widely used as it ought to be, because, owing to the small amount of antibody produced by a localized gonococcal infection, the reaction is generally weak and may often be lacking, and the performance of the test requires the highest skill and the closest attention to details, especially as concerned with the preparation and standardization of the antigen.

It is not the purpose of this review to touch upon the technic of this reaction, as it properly belongs to the domain of the serologist, with special training in this reaction; it is rather our purpose here to consider its limitations and its interpretation and the value which may be placed upon it.

[5] Jour. Am. Med. Assn., 1912, lviii, 931.
[6] Wien. klin. Wchnschr., 1906, xix, 894.
[7] Deutsch. med. Wchnschr., 1906, lxx, 36.
[8] Johns Hopkins Med. Bull., 1907, xviii, 255.
[9] Jour. Med. Research, 1907, xvii, 223.
[10] Ibid., 1910, xxii, 95.
[11] Wollstein: Jour. Exp. Med., 1907, ix, 588.
[12] Jour. Infect. Dis., 1910, vii, 259.
[13] Jour. Royal Army Med. Corps, London, 1914, xxii, 125.
[14] Jour. Canadian Med. Assn., 1916, N. S., iv, 1074.
[15] Schwartz and McNeill: Am. Jour. Med. Sc., 1911, cxli, 693.
[16] Ibid., 1912, cliv, 815.
[17] Ibid., 1912, cliv, 369.

A positive reaction is of far greater value than a negative, which again emphasizes the necessity for the proper interpretation of laboratory procedures. While non-specific reactions have been reported[18] the technic by which they were obtained, particularly as to the antigens used, is not stated in detail and is concomitant with the early days of the reaction, and the majority of observers are in accord in holding that a positive reaction may be looked upon as evidence of an active focus of gonococcal infection.[19 20 21]

Factors influencing the interpretation and reliability of the reaction may be summed up as follows:

1. Because of the small amount of antibody produced, the reaction, when positive, is weaker than the Wassermann and may be indefinite.

2. It is frequently absent in acute, uncomplicated cases,[22] and may not appear earlier than six weeks after the onset.[23]

3. In acute exacerbations of a chronic urethritis the reaction is positive in about 80 per cent. of cases; in ordinary chronic urethritis with mild prostatic involvement, the reaction is positive in 30 to 40 per cent. of cases.[24]

4. The occurrence of an acute complication usually gives rise to a positive reaction.

5. A positive reaction may persist for several weeks after a clinical cure, usually lasting for two or three weeks. If obtained later than that a focus of active infection is probably present.[25]

6. In women the reaction is positive, as a rule, only when the infection reaches the cervical canal. According to Kolmer,[26] in children, positive reactions occur in acute vulvovaginitis, thus evidencing that either the infection is more severe with the consequent production of more antibodies or that the cervical canal is frequently involved.

7. The reaction is positive in about 60 per cent. of pyosalpinx cases.

8. In cases of gonorrheal arthritis the reaction is positive in from 80 per cent. to 100 per cent.

9. The administration of gonococcus vaccine or antigonococcic serum may give rise to a positive reaction which may persist for six to twelve weeks.

10. The reaction has a greater positive than negative value.

It is thus seen there is wide field of usefulness for this test which it is to be hoped, will come into more frequent and common use in the survey of gonococcal infections.

[18] Uhle and Mackinney: New York Med. Jour., 1915, cii, 737.
[19] Thomas and Ivy: Arch. Int. Med., 1914, xiii, 737.
[20] Thomas, Ivy and Beardsall: Surg., Gynec. and Obst., 1914, xix, 390.
[21] Kolmer: Infection, Immunity and Specific Therapy, 1915, 1st ed., 482 et seq.
[22] Thomas and Ivy: Loc. cit.
[23] Kolmer: Infection, Immunity and Specific Therapy, 1915, 1st ed., 482 et seq.
[24] Ibid. [25] Ibid. [26] Ibid.

THE PATHOLOGY AND TREATMENT OF FRACTURES OF THE SPONGY BONES.

By Philip William Nathan, M.D.,
NEW YORK.

(From the Orthopedic Research Department of the Montefiore Home and Hospital for Chronic Invalids.)

Long experience taught surgeons there is no single injury so likely to lead to long-continued or permanent disability as fracture near or through the articular ends of the bones. Now, while the mechanics of the disability are obvious, when a fracture causes such displacement that the articular surface of one bone is no longer con-

Fig. 1.—So-called traumatic flat-foot. The deformity followed an untreated injury, supposedly a sprain.

gruent with its fellow or when hemarthrosis has led to inflammation and secondary adhesions within the articulation, disability which follows these fractures, when such conditions are not evident, has not, so far as I know, been adequately explained. This pertains particularly to the fractures and injuries of the distal parts of the extremities in which the resulting disability is often quite out of proportion to the displacement, and may, indeed, be very considerable without displacement or definite signs of fractures.

The marked inflammatory reaction, the loss of motion and the tendency to valgus deformity, spoken of as traumatic flat-foot,

which follows injuries of the tarsus, is well known and particularly characteristic of this condition. This symptom-complex not infrequently follows apparently insignificant trauma, and as no fracture can be demonstrated, the condition is usually treated as a sprain, which no doubt has led to the prevalence of the belief that sprains of the ankle are more likely to lead to prolonged or permanent disability than fractures elsewhere. Following more violent trauma, with or without fracture, the distortion of the tarsal bones is often

FIG. 2.—Static deformity due to osteoarthritis of the tarsus following severe injury.

extreme and sometimes reproduces the mechanical result of weight-bearing as it would affect the bones were they made of plastic material (Figs. 1 and 2). In the carpal bones, there being no weight-bearing, marked distortion rarely occurs. On the other hand the signs of joint irritation (effusion and spasm, etc.) are equally as common and as characteristic after blows and falls upon the hands and wrists as they are of the foot. Moreover, as detail in the radiograph is more readily obtained, the decalcification and bone absorp-

tion which are the outstanding features of injuries of both carpus and tarsus are more clearly demonstrated. Thus upon examination of the radiographs of the carpal bones a week or more after their injury, especially in the cases without evident fracture or when there is only a fissure without displacement, one is struck by the close resemblance which these pictures bear to those obtained in the inflammatory or infective conditions. In many of the cases all the bones of the carpus, and in not a few some or all of the epiphyseal ends of the phalanges, show the same loss of density which is characteristic of the acute inflammatory conditions of the hand known as acute inflammatory atrophy.

FIG. 3.—So-called Kümmel spine. Traumatic osteoarthritis of the spine following impact of a heavy coil of wire. Unrecognized, though the patient complained, until the deformity became noticeable.

A similar condition occurs in the bones of the vertebræ (first definitely described by Kümmel and known as Kümmel's spine) as a result of blows and falls upon the back. In many of these cases fracture or grave injury of the spine is not suspected until some time after the injury, when the bodies of the vertebræ apparently become softened, a kyphosis develops and symptoms of spondylitis with or without radicular irritation appear (Fig. 3). In some cases fracture of the bodies of one or more vertebræ can be demonstrated, but no

fracture is demonstrable in a considerable number of cases. Practically always the radiograph shows, besides the loss of density, deformation and the definite signs of spondylitis, a spondylitis which cannot be distinguished from that of a non-tuberculous, acute or chronic infective process.

It is not, however, only in the close resemblance of the early radiographic picture that the close analogy between traumatic and non-traumatic inflammatory conditions of the spongy bones manifests itself. Consecutive radiographic examinations of the bodies of the vertebræ, the tarsus and the carpus demonstrate that the radiographic findings after injuries of these bones resemble those due to inflammations and infections not only in the early stages, but in the advanced and terminal stages as well; so much so that in the terminal stages it is almost impossible to distinguish the decalcification, absorption, distortion, lipping, etc., of an arthritis of the spine, the carpus or tarsus, from the conditions due to trauma in those regions.

Nor is the close resemblance between trauma and infection in these bones confined to the radiographic findings. Intra-, peri- and para-articular effusion causing distention of the capsule, compression of the muscles, tendons, nerve fibers and end-organs in the neighborhood of the joint, becoming manifest by swelling, pain, muscular spasm, muscular atrophy and limitation of motion, are equally characteristic of traumatic as they are of non-traumatic conditions. Indeed, so close is the similarity of the two conditions clinically that without a history or a radiograph which actually demonstrates the presence of fracture they cannot be distinguished from each other.

Moreover, though the condition under discussion, which for the sake of brevity may be designated traumatic osteoarthritis, is more readily illustrated as it affects the carpus, the tarsus and the bodies of the vertebræ, it is not characteristic of these bones alone. It occurs in all spongy bones not only in those wholely so constituted, but also in the epiphyseal ends of the long bones which resemble them in structure. These morbid conditions with their attendant arthritic phenomena, as they occur in the shoulder and elbow, are well known. Indeed, the long-delayed recovery and great danger of permanent ankylosis which follow injuries to the elbow are almost classical examples of the condition. The fact that similar changes occur in the hip and knee, however, has not been sufficiently appreciated by the practitioner. That the conditions here are not only analogous to those which occur in the shoulder and elbow, but also analogous to those which occur in the spongy bones generally, seems to have been disregarded or entirely overlooked by all investigators. Yet the similarity of the clinical condition and the radiographic findings in the hip and shoulder and in the elbow and knee to each other and to the conditions in the spongy bones generally is so striking that the analogy between them immediately becomes apparent once the attention is directed thereto.

Thus we have a train of clinical phenomena, which follows trauma near the hip-joint so similar to those characteristic of osteoarthritic conditions that it is quite impossible, without a knowledge of the antecedent trauma, to differentiate one from the other. And this similarity is not confined to the clinical phenomena. The radiographic findings, namely, decalcification, absorption and deformation, with or without hypertrophic changes, are equally characteristic of both traumatic and non-traumatic conditions. In the knee the symptom-complex resulting from injury, as it affects the bones and the soft parts, bears the same striking resemblance to the arthritic conditions.

Evidently then the epiphyseal ends of the long bones and the spongy bones undergo similar pathological changes when subjected to trauma. Obviously this similarity is due to the similarity of the anatomical structure. Hence it may be stated that trauma to the cancellous bones, even when it is not sufficiently great to produce fracture, is likely to induce softening and absorption of the bone trabeculæ, which sometimes appears soon but may not appear until some time after the injury. This pathologic condition under the stress of mechanical factors leads to distortion of the affected bones; it is accompanied by peri- and intra-articular inflammation, and as far as the symptoms and the radiographic findings are concerned, it is apparently analogous to non-traumatic osteoarthritides due to infections or other as yet unknown causes.

In order to demonstrate the pathogenesis of these morbid conditions the following experimental work was undertaken: Six dogs and six adult rabbits were traumatized over the thoracic spine with the steel bar, 6 x 1 x ⅛ inches. In eleven rabbits I tried to produce fracture in the lower femoral epiphysis by indirect violence. Six dogs and six rabbits were traumatized over the great trochanter and the same number and kind of animals over the os calcis with the steel bar. It was found impossible to regulate the trauma over the spine so that actual injury to the bones without fracture could be induced. The injury was either so severe as to induce fracture of the spinous process or lamina or not severe enough to produce actual bone changes.

It was also found difficult to produce fracture near the lower femoral epiphysis without at the same time injuring the knee, but in 6 of the 11 cases I was successful in accomplishing the desired effect. The knee-joint was examined after five days in 2 cases, after nine days in 2 and after eighteen days in the remaining 2 cases. The signs of intra-, peri- and para-articular inflammation were present in all cases examined. There was an exudate which distended the tissues for some distance from the seat of injury, and this exudate was in every way similar to that found in experimental infections. The remarkably early signs of decalcification exactly similar to those which occur in the experimental infections were also found. The affected area was much softer than the normal dog bone and

at times offered very little resistance to the knife. In only one case was there intra-articular extravasation of blood.

Upon microscopic examination, from three to ten days after the injury, the subchondral region adjacent to the site of injury was found to be greatly congested. The bloodvessels were dilated, filled with blood or thrombi and the marrow spaces more or less completely filled with proliferating marrow cells. Later the trabeculæ

FIG. 4.—Traumatic spondylitis. Soldier was hit by a train and treated for sprain of the back for four months. The symptoms were relieved upon the application of a back brace.

make way for the proliferating marrow cells; they apparently become first decalcified and then absorbed, leaving considerable areas within the epiphysis devoid of bony tissue. In two cases the inflammatory reaction involved the articular cartilage. In one the new-formed bloodvessels not only encroached upon but actually penetrated the cartilage, and the joint surface was covered with new-formed evidently proliferating connective tissue (Fig. 5).

In all the rabbits traumatized by a blow with the bar already

mentioned, fracture of the neck of the femur and the os calcis was induced. In dogs with similar injuries no fracture could be demonstrated in the os calcis, but in two cases fracture of the neck of the femur could be demonstrated. In all these animals the changes, namely, marrow hyperplasia, decalcification and absorption, could be demonstrated upon microscopic examinations. In these and in the animals with demonstrable fracture the conditions found were exactly similar to those in the knee-joint and the morbid

FIG. 5.—Traumatic osteoarthritis. Section from the articular surface of the femur, showing the rarefaction (the medullary cells have dropped out of some of the spaces) and a vessel penetrating the joint cartilage. The joint surface is covered with connective tissue.

process differs in no particular (except in the demonstration of the infecting agent) from that which occurs in experimental and accidental infections.

The experimental evidence, therefore, bears out the deductions drawn from the clinical findings; they must lead one to conclude that trauma with and without fracture to the spongy bone, which includes the epiphyseal ends of the long bones, induces inflammatory changes which bear a close resemblance to the non-suppurative infective processes in these structures, and like them leads to bone softening and absorption, which renders them liable to distortion when

subjected to weight-bearing. Like the inflammation due to infection, moreover, the traumatic inflammation is accompanied by intra-, peri- and para-articular exudation and the anatomic changes which are likely to induce chronic or permanent arthritic abnormalities.

The morbid process is due to the trauma acting upon the bone substance and is not secondary to the break in the bone or displacement of the fragments. It is true, of course, that the presence of the fracture indicates a maximal injury, and to a certain extent introduces a complication; the differences in the morbid process, however, when fracture is present and when it is not, are quantitative and not qualitative, the fundamental features remaining the same.

It is not possible to indicate in detail the relations which the facts here elucidated bear to the treatment of these conditions at the present time. Only a few points of general importance can be discussed. As they present the same pathological and mechanical phenomena the traumatic conditions of the spongy bones necessarily present the same problems in regard to the treatment as the non-traumatic arthritides in addition to the problem of reducing and maintaining the fragments in apposition when fracture is present.

Joint motion may be lost or restricted for three reasons: because the displaced fragments produce a mechanical obstruction; because the inflammatory reaction has led to cicatricial contraction, shortening of the tendons and soft parts; or because the decalcification and absorption of the bone trabeculæ, under the stress of mechanical conditions, has led to distortion, and, as a consequence, the joint surfaces are no longer congruent. One or more of these factors may be active in a given case. The fracture and displacement only concern us insofar as their presence complicates the problem of preventing joint ankylosis or the restoration of function. This complication, however, is not nearly as great as is generally supposed. Contrary to the more or less generally accepted opinion very early mobilization is not necessary to preserve the mobility in these cases. On the contrary the inflammatory reaction in or near the joint is alleviated by rest and the fixation required to maintain fragments in apposition is beneficial rather than harmful. It is after the fracture has begun to consolidate, which is approximately the time when the inflammatory reaction has subsided, and only then that mobilization and frequent change of position is likely to promote the early restoration of function. Early and particularly indiscriminate mobilization, far from hastening recovery, in many cases actually retards it. Of this fact I have, as have others, convinced myself many times, in the treatment of fractures and traumas near the elbow. I have found, when I attempted early mobilization, that in not a few cases the elbow which permitted some degrees of motion when mobilization was instituted soon became stiff if I were too insistent. Rest, then, restored the original conditions. I found, then, that it was necessary to judge accurately how soon and to what extent the elbow could be mobilized in a given case in order to

secure the greatest benefit. The same principle holds good as regards the shoulder and wrist.

With some insignificant variations nearly all surgeons now treat fractures of the shoulder in the abducted position. Because of this fact the long and painful after-treatment, which was formerly inevitable in order to restore abduction, is now no longer necessary. But many patients are still subjected to overtreatment and are therefore compelled to endure an unnecessarily prolonged convalescence.

However, though premature mobilization is harmful, fixation cannot be unduly prolonged without predisposing the patient to long-continued or permanent ankylosis. It is plain, then, that it requires judgment, which is only acquired by constant observation and many tentative trials, to determine when and to what extent the joint should be mobilized in these cases. The conditions here are exactly similar to those in the non-traumatic osteoarthritides. In these, too, the injudicious attempts at mobilization often do harm and the auspicious moment when it may begin must be carefully estimated. Often the patient is the best judge of his condition. But this is not always true. There are patients who are too energetic as well as those who are hypersensitive and timid; and it is better to be guided by objective conditions, the relaxation of muscular spasm and the subsidence of swelling, etc., rather than, as has been suggested by a very good authority, upon the subjectivity of the patient.

I am still uncertain as to the utility of massage as an aid in hastening the absorption of the intra- and para-articular exudate. I am certain that it has no influence upon the joint effusion; on the contrary, my experience leads me to believe that even effleurage sometimes causes discomfort in the early stages. That it has any influence upon the exudate in the dense peri- and para-articular structures seems at best problematical. Superheated air, on the other hand, has some value in the treatment of traumatic as well as non-traumatic arthritis. It does not, as many suppose, exert a specific action upon the pathological process; but it does abate the hyper-esthesia and muscular spasm, and in this way forwards passive motion.

In the upper extremity the restoration of the complicated and highly specialized movements is the objective point of the treatment. As weight-bearing is an unusual function the restoration of the bone density need not be considered at all, or its consideration may be deferred. In the lower extremity, however, weight-bearing is a function equally or more important than complete joint motion. The maintenance of the morphologic structure in conformity with the mechanical conditions it must serve and the restoration of the normal bone density at the earliest possible moment are the ends to be sought.

The restoration of joint motion is, of course, to be given con-

sideration. In some cases, however, it is of secondary importance and in others it must be ignored entirely. Thus, as firm union with the maintenance of the normal angle with the shaft is much more important in fractures of the neck of the femur than the motion of the hip-joint, and as good union in this situation is difficult to obtain the future motility of the hip-joint must be ignored and all our energies directed to the treatment of the abnormal bone and mechanical conditions. Hence, as the irritation of weight-bearing with the fragments in alignment is, as far as we know, the only means by which the atrophy of the traumatized and fractured spongy bone can be avoided or the normal density restored, and as this can only be secured by reducing the fracture and maintaining the fragments in apposition by a perfect immobilizing dressing, it is clear that complete immobilization of the femur in the abducted position with actual weight-bearing is the method to be chosen in the treatment of fractures of the neck of the femur. The motion of the hip, which, for reasons which cannot be discussed at the present time, is rarely greatly interfered with in these cases, can and should be completely ignored.

That measures to prevent the distortion of the vertebræ and the resultant deformity are all important in the traumas and fractures of the vertebræ is obvious. When there are no definite signs of fracture these cases nearly always remain untreated until the deformity is evident, when it is, in the majority of cases, impossible to correct. As has been shown the decalcification and bone absorption which follow trauma of the spongy bones, and this seems especially true of the bodies of the vertebræ, often comes on gradually and not until some time after the trauma. For this reason, when there is no fracture, the symptoms and the roentgen-ray changes are often negative immediately or shortly after the accident. It is necessary, therefore, to watch all cases of severe trauma to the back carefully, or, better still, to treat them by rest in bed or immobilization even when the objective signs are negative during the period immediately after the injury. It is necessary, moreover, to continue the immobilization for a rather long time, *i. e.*, for months in the cases with positive findings if recurrence of the symptoms and chronic spondylitis are to be avoided. In the serious cases the immobilization with plaster or a back brace must be continuous; in the milder ones the patient may, without danger, be permitted to remove the brace while he is recumbent.

The treatment of the injuries near the knee- and ankle-joints is somewhat more complicated than those of the hip and spine, for in these situations it is important to secure motility as well as normal density and morphologic conformity. Unfortunately the tendency to ankylosis is much greater in the knee than it is in the hip and spine, which, particularly as regards the knee, often makes it difficult to bring the treatment to an early and successful conclusion. None the less the principles involved in the treatment of the other joints

still hold true; and though it is often difficult to determine when joint motion should begin and to what extent it should be forced, patience and good judgment will often lead to a successful result even in the apparently hopeless cases. Nor is the danger of ankylosis as a result of immobilization any greater here than in any other joints; indeed, the long-continued inactivity to which these patients are usually subjected in order to avoid immobilization is often the cause of greater delay in the restoration of function than would have been the case had immobilization been employed from the beginning. As the various parts, bones, muscles, ligaments, etc., coördinate to perform the function of weight-bearing and locomotion, and as the performance of these functions increases their efficiency, it is evident that the efficiency when lost can only be restored by actual use. The treatment, therefore, which permits of early locomotion and weight-bearing obviously will attain results much more expeditiously than that which requires recumbency. Under these circumstances a splint or dressing which holds the fragments in apposition, and at the same time permits gradually increased weight-bearing, though it necessitates the immobilization of one or more joints, is evidently the method of choice. It is because the danger of muscular atrophy from disuse is supposed to be greatly increased by complete immobilization that the fixation ambulant treatment has been discouraged and long-continued recumbency and complicated mechanotherapeutic measures substituted. It should be understood that actual voluntary movement is the only means of combating muscular atrophy. All the muscles of the limbs are coördinate in action; not one or a few muscles, but practically all the muscles contract (reflexly) when the limb is used in locomotion even when the limb is placed in an immobilizing splint or dressing. For this reason a retention splint or dressing which permits early locomotion not only promotes the restoration of the bone density and allays the inflammatory reaction, but far from inducing muscular atrophy, actually prevents it or forwards the return to normal function.

All things considered, then, provided the fracture is reduced and the fragments held in apposition, immobilization with early locomotion is the treatment which promises the earliest and surest results in the fractures near the joints of the lower extremity. Not only the physiologic and pathologic principles underlying these conditions, which are certainly conclusive, but the experience of many years of practice, with a great preponderance of difficult cases, has forced me to this conclusion.

Another word regarding the fractures and injuries of the tarsus must be added. These closely resemble the traumatic conditions of the spine; that is, the tendency to arthritis and distortion sometimes continues for a considerable time after the injury. These require, therefore, long-continued supervision, and in the majority of the cases a support, preferably a modification of the Whitman plate, which prevents valgus, should be worn for many months.

REVIEWS

THE AMERICAN RED CROSS IN THE GREAT WAR. By HENRY P. DAVISON, Chairman War Council, American Red Cross. Pp. 302; 8 illustrations. New York: The Macmillan Company.

SETTING forth "the scope, character and effect of the work of the American Red Cross during the Great War," the author gives a vivid account of early appeals for support and subsequent relief work in the Allied Armies and in every country of Europe, beginning in 1914 and carrying on after the armistice. Circumstances leading to America's entry into the war and other important events are described in connection with the varied activities of the Red Cross, making the book interesting and valuable as a historical work. The magnitude of the work done by the Red Cross cannot be appreciated through familiarity with only a few of its phases. Mr. Davison, in a very readable narrative, has assembled the facts about welfare work among soldiers and their families, sanitation, care of wounded, relief for non-combatants in stricken countries, communication with prisoners held by the enemy, economic reconstitution, care of children left destitute by the war and other activities in many lands, including Russia and the Near East, besides America and Western Europe. He pays a tribute to the loyalty of all Red Cross workers both at home and in the field, and concludes with an appeal for continued relief activities through the League of Red Cross Societies. T. G. M.

ESSENTIALS OF TROPICAL MEDICINE. By WALTER E. MASTERS, M.D., Medical Officer, Gold Coast, Africa. Pp. 702; 250 illustrations. New York: William Wood & Co.

THIS work is a *vade mecum* for the practitioner and laboratory worker. It contains no new information and does not claim to do so, being rather a digest of present-day knowledge in this field. But in addition to this, it is an expanded note-book in which an experienced and accurate worker has noted down a host of helpful observations.

This book, then, is not for the student who wishes to read up a subject but for the worker who looks up a particular point. To

this end the good index is an important feature. Displayed headings and exaggerated paragraphing enable one to find specific information quickly, but do not make smooth reading. Under each disease the writer summarizes etiology, pathology, symptomatology, diagnosis, prognosis and treatment.

The first section treats of diseases due to protozoa. The most striking feature is a very careful and useful differentiation of the two important amebæ, the various malarial organisms and of kala-azar from oriental sore. Bacillary and helminthic diseases follow, the latter especially well illustrated.

The fourth section is on diseases of uncertain etiology and the next on venoms and poisons, with a great deal of information about snakes. Short sections on the skin and eye are followed by a valuable chapter on tropical hygiene, discussing particularly the question of water supply.

The text concludes with many useful laboratory hints.

The book is of convenient size, well printed and illustrated—the illustrations not original. M. McP.

THE FORM AND FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM. By FREDERICK TILNEY, M.D., and HENRY ALSOP RILEY, M.D. Pp. 944. New York: Paul B. Hoeber, 1921.

THIS is the most important contribution to neurologic literature in years. It is essentially an anatomic work, with a morphologic approach and clinical interpretation. The fundamental concept of the authors is expressed in the second paragraph of the introduction: "The work is designed to fill the gap between morphology and the practical requirements of clinical medicine. It aims to visualize the living nervous system, to make accessible an appreciation of its vital relations to the functions which go to make up life as well as the defects in these relations which result in disease."

It is difficult to adequately review such a large book as this.

Perhaps no American neurologist has had a better preparation for such work than Dr. Tilney, who in the early part of his career devoted most of his time to anatomic research. The fruits of his labors are well known in anatomic literature. It was quite natural, therefore, for him to approach a neurologic problem from the developmental viewpoint. The book is full of original work.

In the opening part there is a general discussion of the conceptions of the nervous system and then the embryologic development is discussed, with uniform excellence. From here the book is devoted to special parts of the nervous system. For example, to the medulla oblongata six chapters are given; to the pons, three, five to the cerebellum and so on, depending upon the importance of the structure. The manner of treatment is equally thorough in each. In the

medulla the encephalization is first discussed; then relations, surface appearance and anatomy; internal structure, histology and finally functional significance and the principal syndromes. This is typical of the treatment of all parts of the nervous system.

The clinical discussion is not by any means the outstanding feature, for the book is essentially anatomical. The method of handling all clinical material is original in the sense that case histories are employed in which in each the clinical history is given and then the anatomic interpretation; the clinical symptoms being illustrated by charts and the pathologic lesion by a photograph of the part, with the location of the lesion standing out prominently, leaving no doubt in the reader's mind as to its localization.

The illustrations are uniformly excellent, there being altogether 591, most of which are original. So far as the subject-matter is concerned it is the best presentation of the anatomy and function of the nervous system in the English language. It is a credit to the authors and to American neurology.

ELECTRICAL TREATMENT. By WILFRED HARRIS, M.D. Pp. 343. New York: William Wood & Co.

THIS is the third edition of this well-known book. A review of the former edition has appeared in this journal. It differs from the former in the fact that the discussion of radium therapy and roentgen-ray treatment have been omitted because both of these have become specialties in themselves. Otherwise, with the exception of a few minor alterations and additions, the book remains what it has been—an excellent manual on the uses of electric apparatus.

REPRESSED EMOTIONS. By ISADOR H. CORIAT, M.D. Pp. 213. New York: Brentano, 1920.

THIS book was evidently written for the lay public and is one of a series of similar books on psychanalysis. While its title is *Repressed Emotions*, it is really an explanation of the principles of psychanalysis. The chapter on repressed emotions in literature is interesting, particularly the discussion of some of the Russian literature and the rather extensive reference to Goncharoff "Oblomoff."

To the psychanalyst this book presents nothing new and to the neurologist it has certain information which can be better obtained elsewhere. To the layman it will undoubtedly be interesting reading, but the reviewer questions the advisability of putting such

a book in the hands of the public, whose interest in sexual literature is morbid. The only excuse for such books is one of propaganda, and in this respect it puts itself on the level of the chiropractor and osteopath. There have been too many books on psychanalysis for the "benefit" of the public in recent years. It seems to be the fashion for psychanalysts and psychologists to write upon psychanalytic subjects.

THE INTERNAL SECRETIONS AND THE NERVOUS SYSTEM. By DR. M. LAIGNEL-LAVASTINE, Paris. Pp. 57. New York and Washington: Nervous and Mental Disease Publishing Company.

THE study of the internal secretions has, in recent years, occupied increasing attention, until now practically every specialty has its own glandular symptomatology and therapeutics. It has been well said that everyone has his own proper physiology and pathology, and that the life of every individual is dominated largely, if not wholly, by his ductless gland chain. To have an adequate knowledge, however, of the function of the ductless glands, one must first of all know the anatomy, especially the physiology, of the vegetative system. The present book concerns itself entirely with the pathology of the internal secretions as they are related to the nervous system.

The author was a pioneer in this field, and this is the only essay on the subject. Consequently the English translation, which is well done, is an important contribution to neurological literature. It is by no means exhaustive and gives merely outlines for study. Perhaps one reason that the subject is not more fully discussed is because the study of the internal secretions is only in its infancy. In the plan of the book there is (1) a general discussion of the vegetative system and the relation of all the generative organs to the nervous system, (2) then there is a discussion of the different glands and the particular diseases related and the disturbances of each, and (3) the diseases and their endocrine symptoms. No neurologist can afford to be without this volume.

HYGIENE OF COMMUNICABLE DISEASES. By FRANCIS M. MUNSON, Lt., M.C., U.S.N., Ret.; Lecturer on Hygiene and Instructor in Military Surgery, School of Medicine, Georgetown University, etc. Pp. 793; 36 illustrations. New York: Paul B. Hoeber.

THE book is divided into two parts. Part I is divided into twenty chapters, deals with epidemiology, prophylaxis and sanitation.

The subjects are completely covered. For example, there are separate chapters on military, naval, railway, municipal, rural, school, prison and industrial sanitation. In addition, in another chapter on exotic hygiene and sanitation, the problems of arctic and tropical sanitation are enumerated. Other chapters that should be mentioned are those on general prophylaxis, infection and immunity, disinfection and disinfectants, insecticides, personal hygiene, hospitals, isolation and quarantine, and especially the interesting consideration of sanitary measures following great disasters.

In Part II the author discusses the separate diseases, first dividing them into classes depending on whether they are fecal-borne, insect-borne, spread by infected animal foods or spread by oral and nasal discharges. Venereal diseases and wound infections each occupy separate chapters.

The illustrations are instructive and helpful. The book presents in concise and readily accessible form the latest facts about the epidemiology of the communicable diseases "ashore and afloat" and their management. A. G. M.

WITH THE DOUGHBOY IN FRANCE. By EDWARD HUNGERFORD. Pp. 291; 8 illustrations. New York: Macmillan Company.

FROM the front-line trenches to the base ports, in hospital, camp and leave area, the doughboy was always able to turn to the American Red Cross for food, shelter, help or pleasure. And how this was made possible, and carried out, and how, also, the French soldier and civilian were taken care of at the same time, is all pictured for us in this very readable book by Mr. Hungerford. P. F. W.

HYGIENE, DENTAL AND GENERAL. By CLAIR ELSMERE TURNER, Assistant Professor of Biology and Public Health in the Massachusetts Institute of Technology; Assistant Professor of Hygiene in the Tufts College Medical and Dental Schools. Pp. 400; 52 illustrations. St. Louis: C. V. Mosby Company.

THIS book is an up-to-date presentation in concise form of the fundamental principles of hygiene, prepared primarily as a textbook for dental students in conformity with the present-day tendency toward education of the dental student on broader medical lines. Its usefulness, however, should by no means be limited to the dentist, for it contains a mass of valuable information for the student of medicine and of public health. Two chapters alone, comprising thirty-seven pages, concern themselves with the

special hygiene of the mouth and oral prophylaxis. The remainder takes up such subjects as diet and dietary diseases, physical exercise, heredity, disease prevention, immunity, communicable diseases, public health administration, school hygiene, ventilation, heating and lighting. Every dental school should give a course in hygiene, and there is no book at present published giving the essentials of a course so suitably as the volume under discussion. R. H. I.

INFECTIOUS DISEASES. By CLAUDE BUCHANAN KER, Medical Superintendent City Hospital, Edinburgh. Second edition. Pp. 627; 32 plates and 68 charts. London: Henry Frowde, Hodder & Stoughton.

THE introductory chapter of this standard and practical textbook is of great interest and only too short. Here various factors related to infectious and contagious diseases are dealt with in abstract. Bacteriology, infection, the incubation period, toxins, immunity, anaphylaxis, fever, the symptoms of fever, the stage of fever, management and treatment of fever, serum and vaccine treatment, diet in fever, diagnosis of eruptions and prophylaxis are the subjects considered. A decidedly fair and impartial mind is displayed by the author. For example, the difficulties of the laboratory worker are recognized—"Even a positive report sent from a laboratory does not necessarily mean that a patient has diphtheria, but that an organism corresponding in its staining properties to the bacillus of that disease, has been successfully isolated."

The diseases considered by separate chapters are measles, rubella, scarlet fever, small-pox, vaccinia, chicken-pox, typhus fever, enteric fever, diphtheria, erysipelas, whooping-cough, mumps, cerebrospinal meningitis. There is also a chapter on fever hospital problems. The author states in the preface that the book is for the most part a record of personal experience supplemented by information gathered from the best sources. Much more than most books is this volume tinctured by personal experience. Especially in the treatment of the diseases is the author frank in telling what he has tried and what has been of value to him. He then gives the conclusions of other authorities.

Illustrations and colored plates are of distinct value in a book of this kind and in Dr. Ker's book the illustrations are many and excellent. The volume could not be otherwise than valuable to any practitioner of medicine. A. G. M.

A Synopsis of Medicine. By Henry Letheby Tidy, M.A., M.D., B.Ch., F.R.C.P., Assistant Physician to St. Thomas's Hospital; Physician to the Great Northern Hospital. Pp. 952. New York: William Wood & Co., 1921.

This book is, as its name implies, a synopsis of the various diseases that one meets in medicine. It gives the essentials of each disease reduced to an irreducible brevity. The volume is not intended for a text-book. Indeed, the author says in the preface that it is only meant for those who have to revise rapidly their knowledge of medicine in general or of some disease in particular. To the student, to the hurried practitioner or to the teacher who has but a few brief minutes to run over his lecture for the day the book will prove of value, and as it is intended for these men, it obviously fulfils the purpose for which it is prepared. J. H. M., Jr.

Cunningham's Manual of Practical Anatomy. Revised and Edited by Arthur Robinson, Professor of Anatomy in the University of Edinburgh. Seventh edition, in three volumes. Vol. I, Superior and Inferior Extremities. Pp. 451; 203 figures. Vol. II, Thorax and Abdomen. Pp. 524; 231 figures. Vol. III, Head and Neck. Pp. 568; 233 figures. New York: William Wood & Co.

In the present edition of this well-known manual the subject-matter is arranged in three volumes instead of in two volumes, as in the previous six editions. The rearrangement has been made necessary by the addition of over 200 pages to the work. This is a striking change, for a comparison of the first and sixth editions shows that they contain practically the same number of pages of text. However, the present increase is due not so much to increase in the printed matter as in the illustrations. At each successive edition there has been an increase in the number of these until now in the seventh edition there are twice the number which appeared in the original work. In the sixth edition 27 plates were added at the end of the volumes, showing roentgen-ray figures of bones and joints, stomach, colon, etc. In the present edition these and other additional figures have been distributed throughout the volumes, in close relation to the descriptive text. In recent years there has been quite generally a reduction in the number of hours allotted to gross anatomy in the medical school curriculum. It will be interesting to see how the change from two to three volumes will affect the popularity of this well-established manual. W. H. F. A.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO,

AND

THOMAS ORDWAY, M.D.,

DEAN OF UNION UNIVERSITY (MEDICAL DEPARTMENT), ALBANY, N. Y.

The Nature of Arthritis and Rheumatoid Conditions.—PEMBERTON *Jour. Am. Med. Assn.*, December 25, 1920, lxxv, 1759-1764). In this report the author offers a working hypothesis of this disease, based on recent reseaches of others and an extensive investigation carried out by him while in government service. He notes that while the importance of focal infection was abundantly illustrated in his cases (young men) still the subjects of the study showed a considerable independence of it. The important role played by exposure and wet alone suggests that focal infection is not the only etiological factor. It may, however, serve as a precipitating factor in these cases. It is noted that agents which hasten metabolism as a whole may have a decidedly beneficial effect on arthritis (*x*-ray, radium, thyroid extract, muscular exercise, psychic disturbances). Moreover, there is in arthritis a difficulty in the utilization of food as indicated by the therapeutic effect of lowered diet and by the frequent presence in these cases of a lowered sugar tolerance. The latter is interpreted as evidence of disturbance of some of the oxidative and combustive processes of the body. Ingestion of carbohydrate in large amounts is sometimes harmful in arthritis. Conversely, the fact that arthritis rarely occurs in diabetes is noted. The fact that rheumatoid conditions occur chiefly in joints and muscles is noted and a partial explanation is offered in that in the joints, on account of their poor blood supply, oxidative metabolism is sluggish, and in the muscles takes place an important part of the metabolism of sugar, one substance known to stand in some relation to the disease. Factors affecting oxidative function are discussed (areas of varying CO_2 tension in the circulating blood; temperature of the blood at a

given point; barometric pressure; factors making for acidosis, etc.). Once the relation of the oxidative functions of the blood to arthritis has been established, these considerations will find application. The author feels that rheumatic and arthritic phenomena find their chief explanation on these principles, and offers the following working hypothesis of the disease: There is a lowered respiratory or metabolic capacity possibly in the circulating blood. This is able to achieve a certain amount of its normal function but not all; those sites therefore at which metabolism is normally most sluggish (joints) are first to suffer. Hyperemia of a part involved often suffices to restore metabolic conditions locally, but does not necessarily relieve the general situation. Thus the disturbance may pass rapidly from one joint to another. That reduction of temperature lowers the dissociation curve of hemoglobins for oxygen is offered as a possible explanation of myositis and arthritis due to exposure. The beneficial effect of heat in arthritis may be explained by the raising of the dissociation curve together with the local hyperemia produced. The author feels that it is reasonable to believe that many factors as many types of infection, exposure to wet or cold, chronic intestinal conditions, possibly interglandular disturbances may induce the substratum, partly illustrated by a lowered sugar tolerance, which is shown to accompany this disease so closely. The paper is concluded with a discussion, along general lines, of treatment.

Failure of Antibody Formation in Leukemia.—Howell (*Arch. Int. Med.*, 1920, xxvi, 706) has made observations upon antibody formation in lymphatic leukemia and in myeloid leukemia with the following results: "Individuals with leukemia who contract typhoid or paratyphoid infection may fail to develop the specific agglutinins in the blood. A similar failure of agglutinin formation also occurs when a leukemic individual is injected with typhoid vaccine in a dosage which causes agglutinin formation in a normal control. Opsonins are also absent in the blood after injection with typhoid vaccine. The failure of both opsonin and agglutinin formation after typhoid vaccination, as shown in the 2 cases reported here, of agglutinin formation in Moreschi's spontaneously infected cases and in his vaccinated cases, and of agglutinin production after vaccination with still another bacterial species, as shown by Rotky, may indicate that the tissues of the leukemic individual have lost the property of antibody formation in general. The loss of ability to form antibodies is probably the result of the marked alterations in the hematopoietic tissues which characterize leukemia. This loss of ability may be due to the excessive proliferation of the hematopoietic tissues, one of whose normal functions is the formation of antibodies. With rapidly repeated cell generations the cellular energy used in multiplication prevents the utilization of the energy which is necessary for normal function. The temperature reaction after bacterial vaccination in leukemia is variable. When a rise in temperature occurs it may not be associated with antibody production. The leukocytic reaction after vaccination is also variable. Some cases react like normals with an increase in the number of circulating leukocytes. Others show no changes. In still others a decrease may occur. The variable leukocytic reaction, like the failure of antibody formation, is probably the result of the alterations in the hematopoietic tissues."

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

Ether; Oil Colonic Anesthesia.—Lathrop (*Jour. Am. Med. Assn.* 72, 2, 82) says he has used this form of anesthesia in 1002 surgical operations, chiefly goiter. The safety of the method is shown by several factors, such as the rate of evaporation of ether from oil, in accordance with well-known physical laws. The ether passes off slowly, especially at body temperature. When the colon is fully distended less ether is absorbed. It is important that the anesthesia be carried on by a trained person. The evening before operation an enema of soap-suds (2 pints) is given. In the morning a second enema of 1 or 2 pints of clear tepid water is given. One and a half hours before operation 2 drams of olive oil (warm) and 3 drams of paraldehyde and 4 drams of ether are given. Twenty minutes later morphin sulphate, grain $\frac{1}{4}$, and atropin sulphate, gr. $\frac{1}{150}$, are given hypodermically. Thirty minutes later 3 or 4 ounces of ether and 2 ounces of olive oil (warm) are given. The oil and ether are shaken thoroughly before introduction into the rectum. The patient should be on the left side with both knees flexed, the right acutely. A rectal or colon tube is inserted not more than six inches after all air has been excluded. The mouth and nose are covered with several thicknesses of gauze. The mixture should be given slowly, about 1 ounce a minute. The funnel attached to the tube should be held about 3 inches above the level of the patient. The tube should be clamped and allowed to remain in the rectum so as to be able to withdraw the mixture if desired. If the patient cannot retain the mixture one should not try to repeat the procedure. The patient should be ready for operation in from twenty to thirty minutes from the time of the last injection. The reversed Trendelenburg position seems to aid in maintaining an even plane of anesthesia. When the operation is completed the bowel should be irrigated with tepid water until the water returns clear. One pint is then put in the bowel and left or 4 ounces of oil may be used. The author finds the method most useful in toxic goiters and has used it extensively in these cases. The method is contraindicated in rectal diseases or when pain is caused by its introduction.

Fracture-dislocations of the Ankle.—Roulands (*British Med. Jour.*, December 6, 1919, p. 1575) says these serious accidents are commonly followed by bad results. It is a common mistake to regard a fracture of the lower part of the fibula without any displacement at the ankle as a Pott's fracture. In a typical Pott's fracture the fibula is broken in the lower third and either the internal malleolus is detached from the tibia or the internal lateral ligament is torn. This allows a rotation on the

inferior tibiofibular articulation. The outer edge of the superior articular surface of the astragalus becomes uppermost and is drawn backward. In a Dupuytren fracture we have the lesion already described plus a tearing of the inferior tibiofibular ligaments or a vertical fracture in the tibia just mesial to the tibiofibular articulation. The outer and upper wedge of the rotated astragalus then becomes the apex of the wedge which increases the separation of the tibia and fibula. This separation also occurs in oblique upward and outward fractures of the fibula from just below the inferior tibiofibular articulation. Rouland believes these fracture-dislocations are some of the most serious injuries of the lower limbs, since the abduction, eversion and flattening of the foot increase with time. Osteo-arthritic changes soon take place in the ankle and metatarsal joints and later the knee and hip may become affected. In all roentgen-ray examinations, and these are essential, the ankle should be examined in both the anterior posterior and the lateral position. The complete reduction is difficult and only by operation can the fragments be brought into perfect apposition. There are different views as to the necessity of getting perfect apposition. When treated conservatively an anesthetic should be given in order to properly reduce the fracture. In some cases division of the tendo Achillis is warranted. Reduction should not be attempted after swelling has appeared until it subsides. It is easier to maintain a good position with a plaster splint than by any other means. Roentgen-ray examination should be repeated. After three weeks massage and passive movements begin. No weight-bearing is allowed for eight weeks and the inner border of the boot is built up when this begins. When the above method fails to get a good reduction operation can be done within one week of the accident. The fibular fracture is wired or plated. The tibiofibular separation is corrected with a long screw. In many cases this is all that is required. The long screw has been retained by many for years. Correction of the deformity and restoration of function in late cases is difficult. The tendo Achillis must frequently be divided at operation, and this is best done by dividing the two lateral halves at two levels. The tibia is divided three-fourths of an inch above the level of the tip of the malleolus and the deformity slightly overcorrected. The after-treatment is similar to that given under conservative treatment.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

Immunization against Diphtheria in a Large Child-caring Institution.—BLUM (*Am. Jour. Dis. Children*, July, 1920) made Schick tests in 1076 children in an institution during a period of five years. He found that a negative Schick test is evidence of the presence of sufficient antitoxin in the tissues to protect the individual against diphtheria infection. The

moderate or slightly positive test denotes an insufficient amount of antitoxin in the tissues to protect the individual. The tests called very faintly positive show possibly sufficient antitoxin to protect, but it is possible to transfer virulent organisms to these individuals, which may not only cause them to become carriers, but may cause them to suffer from a superficial infection without any constitutional toxemia. Tests made on 72 families showed that the younger members of the same family usually gave corresponding reactions to the Schick test. When variations did occur the younger members gave usually the positive and the older the negative reactions. Infants under six months of age because of the transmitted immunity from the mother were exceptions to the rule. Change in the Schick reaction from negative to positive during the first three years of life, due to the loss of inherited immunity, were found to be sufficiently numerous to justify retesting during this period, at intervals of a few months. The full duration of the active immunity conferred on individuals susceptible to diphtheria by the injection of toxin-antitoxin is not yet ascertained. In one series the immunity persisted in 100 per cent. of the cases of a group of 50 children for at least twenty-two months. Once acquired, immunity may last for four and a half years. The institution in which this study was conducted has been kept free from diphtheria for a period of five years.

A Study of the Malnutrition of School Children.—Brown (*Jour. Am. Med Assn.*, July 3, 1920) made a study of the children of a school in which 41 per cent. of the pupils were at least 10 per cent. under weight. She found that the two factors chiefly responsible for the beneficial results were the work of the school nurse in securing home coöperation and the selection of food with reference to supplying the dietary deficiencies of the home. One of the most interesting observations was that these children readily stowed away from 1000 to 1800 calories in addition to their customary three meals. The mothers reported that they ate more at home as well. This indicates that the amount of food needed by growing children has been underestimated. No correlation was found between the rate of growth of these children and any social conditions. The time of the observation was too short to show the favorable results of the other elements of the health service. If a few weeks longer had elapsed it is probable that a favorable result would have been shown by the correction of dental defects and the removal of diseased tonsils and adenoids. Two facts stood out. These children in spite of adverse conditions and handicaps were so badly in need of food that they made a gain of 278 per cent., or 302 per cent. gain over a control group. Nine and half months of intensive health service brought this school from the lowest rank in the city to third place.

Precipitins for Egg Albumen in Stools.—Grulee (*Am. Jour. Dis. Children*, July, 1920) studied the stools of three groups of cases to ascertain the digestion of egg albumen. In the first group 103 stools from 24 cases were examined, with three positive reactions. These were all from children of two years or over. Two of the positive reactions occurred in a case of idiocy. This child took large quantities of egg in the diet while the other children in this series were only given

egg in ice-cream or puddings once or twice a week. The other positive reaction occurred in the stool of a case within forty-eight hours after taking the diet. In seventeen other stools from the same case no positive reaction occurred. In the second group a teaspoonful of egg albumen was given each day to a control case through a gastrostomy wound, to a case of intestinal infantilism and to a case of general eczema. In seventeen stools from these cases only one showed a doubtful reaction. The third group of 33 cases of infants of two years or under, furnished 221 stools. In only two of these cases was the age over one year. Many were newborn infants who had received albumen water of a strength of 10 c.c. of egg albumen to 500 c.c. of water. Five stools gave positive reactions. One of these occurred in a newborn infant. In the other three children there was no albumen in the diet. From this observation it is seen that egg albumen is nearly always completely broken down by the digestive processes of infants and children.

The Effect of Splenectomy upon Growth in the Young.—HENN (*Am. Jour. Physiol.*, July, 1920) says in this work that the results of observations on rats and rabbits are sufficient to permit of conclusions as to the effect of splenectomy upon growth. He felt that he was not justified in drawing conclusions upon the results of his two series of experiments on kittens, although their weight curves were similar to those of rats and rabbits. In dogs there were early influences of distemper and gastro-intestinal disturbances that presented a factor that was not ruled out in other animals. The resistance of blood corpuscles to hypotonic sodium chloride solutions was found to be true in animals operated upon while young as well as in others operated when older. This suggests that the spleen may have the function of preparing the blood for destruction. The quickened coagulation of the blood from splenectomized dogs may be a protective means against the loss by hemorrhage during the time of the anemia. The results suggest that the earlier that an animal is splenectomized the more rapid is the time of coagulation. It may be due to the general leukocytosis or to an increased amount of fibrinogen, which may account for the large amount of fibrin secured when the blood from splenectomized animals is defibrinated. This increase of fibrinogen may be due to a greater production by the liver in the absence of the spleen. No difference was noted in activity or temperament in rat, rabbit or dogs, but a slight difference was seen in kittens. This may be due to some individual variation rather than to any effect following removal of the spleen. In rabbits it was clear that the females were not rendered sterile. In rats neither sex was sterilized. Histological examinations suggested that the spleen was somehow connected with the blood. The presence of large hemolymph glands, especially in the mesentery, suggested that if this was a compensatory hyperplasia following splenectomy it is important that such a function should be produced in the portal circulation. The bone-marrow changes were striking. The bone-marrow through the different types of cells present indicated that there was a process of erythrogenesis and leukogenesis taking place while an increase of Kupffer cells and endothelial cells of lymph glands indicated a process of blood-destruction.

The Treatment of Indigestion in Children—Morse (*Jour. Am. Med. Assn.*, July 10, 1920) says that there is no place for the so-called digestants in the treatment of chronic indigestion in children. There is probably never an insufficiency of hydrochloric acid or pepsin, and as pancreatin is destroyed in the stomach it can be of no use. The main essentials of treatment consist primarily in regulation of the diet to fit the digestive capacity of the individual child. Examination of the stools is of importance in controlling this factor. In the cases in which there is marked clinical evidence of fermentation, bacteria undoubtedly play an important role. In cases in which the evidence of fermentation is less they may also be an important cause of trouble. It is of the greatest importance that bacterial activity be limited. He says that it is impossible to change the intestinal bacterial flora by giving bacteria by mouth, although it may be temporarily limited by the continuous administration after this manner. The best way is by changing the composition of the food. Diminishing the proportion of the carbohydrates and increasing that of the proteins changes the flora from the fermentative to the putrefactive, and by doing the reverse the flora may be changed fron the putrefactive to the fermentative. This can be shown by bacterial examination of the stools, but can be as readily shown by the reaction of the stools, as the stools are acid when the flora is mainly fermentative and alkaline when the flora is mainly putrefactive. Organisms growing on fat have relatively little to do with fermentation in the intestinal tract, but the products of their activity increase the activity of the stools. When the organisms of the gas bacillus group are the cause of the fermentation of the intestinal contents much may be done by the administration of the organisms that produce lactic acid. The best type is Bacillus bulgaricus, and the best results are obtained when it is given in the form of buttermilk. In addition to a greater number of bacteria the buttermilk contains considerable lactic acid. There is no place for drugs except for temporary relief.

Frozen Milk.—Mixsell (*Arch. Ped.*, May, 1920) presents a problem about which the physician is frequently questioned, especially in our Northern States, during the winter months. Owing to the marked difference of opinion of authorities he makes it a rule to use some other feeding if the milk has become frozen. This is especially done in the case of young infants. He states that he has never seen personally any deleterious effects from the ingestion of frozen milk. It is perfectly possible that a putrefactive diarrhea may ensue, owing to the growth of the putrefying bacteria at low temperature and the breaking down of the proteids into amino-acids, or to have a diarrhea as the result of lactic and fatty acid formation. It has been shown that there is no increase in the number of bacteria in forty-eight hours. After that time the increase is marked, although the usual lactic acid forming organisms are not present in sufficient quantities to form a curd. There is rapid proteolysis which is pronounced at the end of two weeks. The acidity is markedly increased, owing to the bactericidal action on lactose changing it to lactic acid. No marked change in the fat has been noted except that caused by bacteria.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

The Use and Abuse of Castor Oil.—In the *Journal of the American Medical Association*, November 29, 1919, occurs an editorial on this subject. It must be remembered that castor oil contains an irritant substance, ricinoleic acid, which is produced by the digestion of the oil in the intestine. This excites peristalsis, causing the small intestine to empty itself into the colon in two hours, instead of in the normal eight. Castor oil contains an unsaturated fat acid which is absorbed and may be assimilated and become of food value. It is an article of diet in China. The action of castor oil is somewhat independent of the dose, and the dose is not much influenced by the age of the patient. An infant may safely have a teaspoonful or two of castor oil, although this dose will usually cause a marked result in the adult. When the oil is not entirely digested the undigested portion passes through the bowel as a lubricant, acting like petrolatum. Excessive action of castor oil is practically impossible. When, therefore, there is difficulty in giving an adult person one or two tablespoonfuls it must be remembered that satisfactory results are frequently obtained with very much smaller dose. Because of its thoroughness and reliability of action the impossibility of excessive effect and usually its lack of irritation castor oil is greatly used by pregnant women. It rarely causes intestinal griping and so is a good remedy for intestinal colic. Daily doses of castor oil have often relieved obscure abdominal pain and chronic irritation of the intestine. When intestinal obstruction is suspected castor oil is probably the least objectionable of the reliable cathartics. If a liberal dose fails to act drastic purgatives should be avoided. One of the objections to the use of this substance is the fact that in most cases it leaves the bowels sluggish after it has produced an evacuation. In chronic constipation it is one of the worst drugs. Because of its soothing qualities it is often the best possible substance in cases of irritant diarrhea. Doses (teaspoonful) of it produce no irritation, and when compared with magnesium sulphate and calomel castor oil seems to have the least irritating action. A dose usually acts in from four to six hours. It has a tendency to delay function of the stomach, and is best given on an empty stomach an hour before breakfast. It is possible to so refine castor oil, if it be protected from the influence of the air, that it is almost devoid of odor and taste. Such oil should be procured in bottles, used while fresh and the bottle kept carefully corked. Elastic capsules furnish an excellent medium for the administration of castor oil, 2.5 c.c. being none too much for adult persons. These capsules may be swallowed more easily if they are dipped in water for a moment just before taking, and if the patient will look down while swallowing, as he does while eating his food, the capsule will pass down more readily. Holding the head up while attempting to take pills or capsules is a frequent cause of inability

to swallow them. Two of these capsules usually give a very good result. If a much larger amount is required it is best given in the form of the so-called sandwich. Such a sandwich is prepared by placing in a small tumbler or medicine glass a layer of thick syrup of any flavor desired. The glass is inclined in such a manner as to coat its inside almost up to the rim with the syrup. The oil is poured into the center of the glass, care being taken that it does not run down the side. Over the oil is put a layer of aromatic elixir, and while the dose is being taken the edge of the glass should be placed in the lower teeth to avoid straining the oil through the teeth, as some will adhere and occasion an unpleasant taste. A newborn infant needs no disguise for castor oil. The taste sensation in the infant is not well developed at birth. When, however, the child begins to taste the oil as it grows the oil should be disguised. If possible a day's fasting is an excellent preparation for the action of castor oil in children. Some children will take oil better if it be sweetened and if aromatics are added to it. Saccharin dissolved in alcohol will sweeten castor oil very pleasantly. Aromatics may then be added which greatly improve the taste and action. It is sometimes necessary to administer castor oil without the knowledge of the patient. If the so-called tasteless oil is shaken vigorously with four times its quantity of hot milk, and if the dose be taken immediately, it is practically tasteless or has the pleasant taste of the aromatics employed. Such oil might also be given floating on hot soup. Care must be taken not to excite a prejudice against some article of food by mixing it with castor oil. Emulsification lessens the activity of this substance, probably because in this form it is too rapidly digested and assimilated. A 35 per cent. emulsion of castor oil is palatable and can readily be made. It may be flavored with tincture of vanilla. In the observation of the reviewer a child was given castor oil mixed with the yolk of a raw egg; this created such disgust for eggs that the patient, now a grown woman, has never been able to take them. Castor oil has at present a considerable reputation in inducing labor in pregnant women. There is no objection to its use, but it will often fail utterly to accomplish its purpose. It should be given at night, disguised with fruit juices, aromatics or a small quantity of whisky or brandy. The action of the oil upon the bowel is greatly enhanced by high colonic irrigation on the following morning. For the induction of labor, quinin is frequently given with castor oil, and then it may be difficult to determine if labor begins which drug has been efficient. In pregnancy, in the puerperal state, the administration of castor oil repeatedly tends to make the bowel sluggish and hence for habitual action is not to be preferred. Compound licorice powder is agreeable to most persons and produces a better result nor does it in the pregnant person seem to lose its effect. Castor oil is employed by some as an application to the nipple of the pregnant woman to prepare the nipples for nursing. It may be combined with some substance which is astringent and castor oil and bismuth is a combination considerably used.

Premonitory Signs of Eclampsia.—Van Cauwenvenge (*Revue franc. de gynec. d'obst.*, August, 1919) believes that eclampsia may be imminent in a patient whose urine is apparently normal. There will, however, have been digestive disturbances in such a patient, and frequently

intractable vomiting. It may be necessary to bleed such patients, for if the woman comes into labor she should be allowed to lose a reasonable quantity of blood. Pituitary extract should be avoided in the management of these cases. In one of five recent cases of eclampsia a primipara of eighteen had no symptoms whatever except a little pain in the stomach when eclampsia developed. In one, except for two periods of vomiting, one early and one late in pregnancy, the conditions were normal, but the patient died in convulsions. Another patient had inertia of the uterus, accompanied by frequent vomiting, and was given pituitrin. The delivery was rapid, but the uterus kept contracting for forty-eight hours after labor, and there was scarcely any of the normal blood loss. Thirteen hours later cramps developed in the stomach, followed in four hours by convulsions and coma, but the woman recovered. In two previous pregnancies she had vomiting, but no eclampsia. In her last delivery the pituitary extract had locked up the uterus so that the usual loss of blood did not occur, thus producing congestion, and the accumulation of poisoned blood had produced eclampsia. Very probably the immediate factor in this result was the intense uterine contractions which the patient had. In the fifth case the patient had no albuminuria, but when labor came on there were headaches, disturbances of vision and a little edema in the feet. Expulsion was rapid and a considerable quantity of blood was lost. This persisted, but was not checked, and very soon the patient's headaches subsided and her symptoms disappeared. The writer is convinced that this hemorrhage saved her from eclampsia.

The Justo-minor Pelvis.—DANLIN (*Revue franc. d. gynec. d'obst.*, August, 1919) by this term describes a pelvis that is too narrow in a patient otherwise well formed. Sometimes the type of pelvis is adult, but unusually small, or it may be funnel-shaped, of the infantile type. The hips are narrow, the measurement from crest to crest 24 or 25 cm. instead of 28, and between the spines 18 to 21 cm. These patients menstruate late and there is some disturbance of the ductless glands, and this causes a premature junction of the points of ossification, which stops the growth of the pelvis just as the premature closing of the fontanelle stops the growth of the skull. The obstetrician can usually be warned of this condition by external measurements and by the use of the roentgen ray. Induced labor should be avoided in these patients and Cesarean section at term if the conjugate diameter is 9 cm. or less is far better. If the obstetrician attempts to deliver through the vagina the use of forceps is better than version. The head should be in the oblique diameter and a pair of forceps should be chosen which fits the head well. In this type of pelvis the difficulty increases as labor proceeds.

Prolapse of the Uterus in Pregnancy.—BERNALDEZ (*Jour. Med. Ibra.* special number, 1919) records the case of a multipara who had suffered in her first labor a complete tear of the pelvic floor which had never been closed. She had afterward two labors. In the fourth pregnancy she had complete prolapse of the uterus. The entire womb had descended through this enormous tear, but the symptom which most distressed the patient was retention of urine. The bladder could be emptied by catheter, but the lack of support of the ligaments by the

pelvic floor was such that it was impossible to reduce the uterus. As the result of the exposure and constant irritation the cervix was deeply congested and ulcerated. The question of treatment was a difficult one. It was impossible to keep the uterus in place by the use of tampons while the pregnancy continued. As the cervix was infected it was dangerous to bring on labor. If the uterus was to be entirely removed an abdominal section was inevitable and this might cause fatal peritonitis. The patient had a spontaneous abortion, but passed out of observation and her subsequent history is unknown. In a somewhat similar case the reviewer kept the patient in bed for two months before delivery, using antiseptic solutions upon the cervix and sterile dressings. In this way the infection and inflammation largely subsided and the patient passed through a spontaneous labor successfully. She was afterward subjected to operation.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Value of Smears in Diagnosis of Gonorrhea.—When dealing with inflammatory lesions of the lower genital tract it is advantageous to determine the type of infection present, but NORRIS and MICKELBERG (*Jour. Am. Med. Assn.*, 1921, lxxvi, 164) point out that during the acute stage of the gonococcal infection the diagnosis is generally made without difficulty, as the clinical signs are more or less significant; if doubt exists, film preparations can be depended on. During the chronic stage the clinical signs are less characteristic than during the acute stage and the examination of smears is also less satisfactory. The presence of gonococci can be demonstrated by film preparations from every case if a sufficient number of correctly performed examinations are made. A single negative smear examination is without significance. In such a case the chances of demonstrating gonococci are about three or five to one according to the skill of the examiner and even under the most favorable circumstances, positive film examinations can be obtained in only a relatively small proportion of cases. Unless safeguarded by the Gram stain, smear examinations are valueless and even with Gram's stain errors in diagnosis may occur since differences in the thickness of the preparations, slight overstaining or understaining, etc., may lead to extremely misleading results. Owing to the many difficulties surrounding this form of diagnosis, the authors believe that unless the test is performed by one experienced in the

work, its results are of no value and are often actually misleading. They believe that clinical evidence is of far greater value than staining methods, even when the latter are performed by an expert and from a practical standpoint all cases should be regarded as of gonococcal origin until proved otherwise.

Management of Cervical Stump.—BISSELL (*Surg., Gynec. and Obst.*, 1920, xxxi, 578) is firmly opposed to the common practice of anchoring the round and broad ligaments to the cervical stump in the performance of supravaginal hysterectomy, on the ground that such practice displaces the stump and does not hold it in its proper position as it is supposed to do. In the follow-up clinic of the Woman's Hospital he has examined 130 cases of supravaginal hysterectomy done without anchoring the round ligaments in the cervical stump. In 127 of these cases the cervix was in normal or practically normal position prior to operation, and in not a single instance was the cervix found prolapsed after operation. In 3 cases the cervix following operation was found prolapsed with considerable relaxation of the anterior vaginal wall. In each instance, however, the conditions existed prior to operation: two of these cases were operated upon a second time, the cervix in each instance was removed and the fascia of the anterior wall lapped. The results in these cases were successful while the third case is awaiting operation. Bissell believes, therefore, that the condition of the pelvic floor is of much more importance in maintaining the cervix in its proper position than the anchorage of the stump to the ligaments, which procedure tends to displace the stump forward.

Treatment of Fibroid Tumors.—The conscientious and thoughtful operator makes every effort to preserve the menstrual function of his patient when dealing with fibroid tumors of the uterus. VINEBERG (*Med. Rec.*, 1921, xcix, 91) insists upon the importance of preservation of the menstrual function, for the ovaries, to his mind, serve no useful purpose when the uterus has been removed or when the endometrium has been destroyed, so that menstruation is no longer possible. Some of the very worst cases of the artificial menopause syndrome have been witnessed in women who had their ovaries and their uterus *in situ*, but in whom a too energetic curettage had brought about a permanent cessation of menstruation. The same applies to instances when the uterus was removed and the ovaries left behind. There is to be observed at the present time a singular state of mind on the part of the medical men. They are all keenly alive to the importance of conserving the menstrual function in women. They hesitate, to their credit, to consign their patients to an operation which would destroy that function. Still they will refer, without a moment's hesitation, a patient with a bleeding fibroid of the uterus, to the roentgenologist or radiologist, who can only be successful in destroying that function and, in most instances, permanently. Every patient who consults the writer regarding a fibroid tumor causing symptoms is told that she may have her choice of treatment, either by operation or by roentgen ray or radium. He tells her, regardless of her age, that the one (operation) perhaps carries more risk with it than do the others, but that in his opinion it is a more certain, permanent cure. If she is under forty he tries to impress her

with the advantages, of which he is strongly convinced, of submitting to an operation, the endeavor of which would be to remove her tumor or tumors and preserve her menstrual function. In spite of our strongest determination and most painstaking efforts, it must be admitted cases will now and then be encountered in which it is not possible to save the uterus. What we must endeavor to do, then, is to save enough of the organ and endometrium to carry on the function of menstruation. Even should we be baffled in this, and the entire organ have to be sacrificed, the patient would in no wise be any worse off regarding her menstrual function than she would have been had she been successfully treated with roentgen ray or radium. On the contrary, the writer believes she would be better off, for her cure would be more certain and more complete.

Action of Emmenagogue Oils on the Uterus.—Some experiments which have been performed on the isolated human uterus by GUNN (*Jour. Pharm. and Exp. Ther.*, 1921, xvi, 485) to determine the action of emmenagogue oils agree with the results of other observers on the excised uterus of other mammalia. It would seem that the emmenagogue oils in very small amounts have no action at all on the uterus. In higher concentrations such as never could be reached in the blood without producing dangerous, probably fatal, poisoning, they inhibit the uterine movements. When abortion occurs after their use it is probably an indirect result of severe irritation and inflammation of the bowel and kidney. This may induce congestion and reflex movements of the uterus which may in some cases result in abortion. The absence of specific stimulant action of these oils on the uterus renders them all the more dangerous poisons, as, after their failure in ordinary doses, large doses are sometimes taken, resulting in frequent poisoning, in a large proportion of cases, without the production of abortion.

Gynecologic Backache.—A small volume might be written about backache if this symptom were studied exhaustively from every viewpoint, and a most interesting and instructive treatise it would be. Probably the longest chapter should be written by the orthopedist, but the gynecologist, neurologist and internist could contribute much interesting material, and so interdependent should these be that the authors would do well to consult each other freely in the preparation of their respective monographs. Some surprising observations made in the postoperative follow-up clinic at the Woman's Hospital in New York during the past few years led BULLARD (*New York Med. Jour.*, 1921, cxiii, 142) to feel that an analytic study of backache would be interesting. As a result of such an investigation he found that in a series of 721 cases of backache studied, 85 per cent. were cured by an appropriate operation. About 15 per cent. of this series presenting one or more common gynecologic causes of backache were not relieved of the backache by anatomically satisfactory operations. Probably much more than 15 per cent. of the backache in females is not gynecological. This study suggests that 15 to 20 per cent. of all women with retroversion, prolapse, pelvic, inflammation, obstetrical lacerations, or pelvic tumors, do not have backache. Closer coöperation with the orthopedist, internist and the neurologist should enable the gynecologist better to diagnose and treat backache in women.

Tuberculosis of the Kidney in Women.—The results of an analytic study of renal tuberculosis in women made by BRADY (*Bull. Johns Hopkins Hosp.*, 1921, xxxii, 13), of the Johns Hopkins Hospital, shows that in a series of 77 patients, 25, or 32 per cent., of the patients complained of hematuria, and in 8 of these it was the first symptom. Two patients first noticed general weakness, and in all the other cases dysuria and pyuria were the first evidences of kidney disease. The general physical examination showed pulmonary tuberculosis in 6 cases. Four of these patients had active, two inactive, pulmonary tuberculosis. One patient developed tuberculous peritonitis two years after the removal of a tuberculous kidney. In 4 cases only was a marked enlargement of the kidney noted, and in all these cases operation revealed that they were dealing with cases of tuberculous pyelonephrosis. The routine gynecologic pelvic examination showed the ureter to be thickened and tender in 23 cases. This nodular thickening, with tenderness of the portion of the ureter which can be felt on vaginal examination, has been of great help in promptly directing attention to the probability of tuberculosis in the urinary tract. In 5 cases surgical treatment was not advised and in 2 others was refused by the patient. Four of these women had tuberculosis of both kidneys, one with symptoms dating back eight years, the second two years, the third one year, and the fourth only eight months. One of these women died in three months, the second in six months, the third in one year, and the fourth left the hospital unimproved and has not been heard of since. One woman had a unilateral renal tuberculosis, with advanced pulmonary changes, and in her case operation was not advised; she also left the hospital unimproved and has since not been heard of. In the two operable cases in which surgical treatment was refused the patients died within one year after leaving the hospital. In 70 out of the 77 cases operations were performed. In 67 cases the kidney was removed and in 3 cases simple nephrotomies were done. The results obtained in these 3 cases are very discouraging. One woman died in three months, a second in two years, a third left the hospital unimproved and has not been heard of since. This means that 8, or 19.5 per cent., of the 42 women of whom the records are complete are now dead. These 8 patients lived, on an average, for three years after their operation. Two of the living patients are unimproved, one three, the other nine years after operation. Seven may be classed as greatly improved. These seven women are all able to carry on their daily occupations and complain of slight bladder symptoms. Twenty-five, or 59.5 per cent. of these women, whose present condition is known are entirely well, with an average of eleven years since their operation. In this series there is one woman operated on twenty-four years ago, another twenty-two years ago and two twenty years ago. These patients have been relieved of all their symptoms by operation and report themselves to be now in good general health. Brady has divided all the cases in which the final results are known into two classes, one formed by those women from whom only the kidney was removed and the other by those from whom as much of the ureter as possible was removed at the same time. After careful study, the writer has been unable to show that the removal of the ureter makes any difference in the ultimate results of the operation. Approximately 19 per cent. of both groups of patients are now dead, 5 per cent.

are unimproved and 76 per cent. are either greatly improved or well. This study, however, has shown that the postoperative sinuses of the patients on whom nephro-ureterectomies were performed healed in an average time of five months, whereas the women in whom the diseased ureters were left, drained for eleven months. From this it would appear that it is better to remove the ureter along with the kidney when the condition of the patient warrants prolonging the anesthetic the short time necessary for carrying out this procedure.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

DIRECTOR OF THE PATHOLOGICAL LABORATORIES, SAO PAULO, BRAZIL,

AND

DEWAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

Studies on Experimental Pneumonia.—The experimental study of lobar pneumonia has long been hampered by the difficulty surrounding the production of this disease in animals. The various attempts at introducing bacteria into the deeper air passages by insufflation and by injection in fluid suspension have resulted in bronchopneumonias. Even the highly artificial method of flooding the lung with a suspension of bacteria failed to produce the typical lobar pneumonia. Following a method used by Opie and others in unpublished experiments, BLAKE and CECIL (i, *Jour. Exper. Med.*, 1920, xxxi, 403) were able to produce typical lobar pneumonias in monkeys. The method was by inserting a dry, sterile needle into the trachea and injecting very small doses of living, virulent pneumococci. The organisms were always suspended in 1 c.c. of fluid. All the biological types of pneumococci were employed. The following is a brief summary of the results obtained with the different biological groups of pneumococci: Out of 31 monkeys injected with type, i, 26 took lobar pneumonia. Out of 2 monkeys injected with type ii, 2 took lobar pneumonia. Out of 3 monkeys injected with type iii, 3 took lobar pneumonia. Out of 4 monkeys injected with type iv, 1 took lobar pneumonia. All monkeys injected with types ii, iii and iv recovered. Out of 6 monkeys exposed to contact infection only 1 developed lobar pneumonia. Inoculation of pneumococci into the nose and throat induced a carrier state but none of these animals contracted lobar pneumonia, nor did they develop any infection of the upper respiratory tract. Subcutaneous and intravenous injection of pneumococci did not produce lobar pneumonia. Invasion of the blood stream by pneumococci was demonstrated to be secondary to the infection of the lung. They have shown, therefore, that lobar pneumonia is bronchiogenic in origin. Pneumococci were isolated from the blood stream within six hours after the intratracheal

injection. The methods of study after inoculation were similar to the ordinary clinical methods. They consisted in observation and record of clinical symptoms and physical signs, with temperature records made twice daily and daily white cell and differential blood counts, and blood cultures. These records were in every way comparable to those obtained in the course of a lobar pneumonia in the human. Autopsies on the animals that died and on others killed at selected intervals furnished the material for the experimental study of the pathology of the disease. In the report of this work (ii, *Jour. Exper. Med.*, 1920, xxxi, 445) is included the study of 40 autopsies on monkeys. Of these 27 died during the active stage of the disease, or from complications, and 13 were killed at varying intervals following the crisis. This series of animals permitted study of the lungs at intervals of one to twenty-three days after the onset of the disease. This series presented examples of the four classical stages of the disease. Animals dying within five days after intratracheal injection showed either engorgement or red hepatization. The later stages have been thoroughly studied in human material. It is from the study of the early stages that this phase of the problem attains its chief interest. Microscopic examination showed that while the infection invades by the bronchiogenic route, it soon becomes interstitial at some point near the hilus of the lung, producing an early, acute inflammatory reaction in the vascular adventitia and walls of the bronchi near the root of a lobe. This is accompanied by edema and a leukocytic infiltration of the interstitial tissues and by intense capillary engorgement. At this stage bacteria were found to spread rapidly throughout the lung, following the ramifications of the vascular and bronchial trees and appearing always to precede cellular exudation into the alveoli. In the same way hepatization was found to spread throughout the lobe from the region of the hilus to the periphery. During this early process the epithelium of the bronchial tree appears fairly intact and the air passages contain little or no exudate. After the five-day period, in which time the stage of red hepatization has developed, the more familiar histological pictures of lobar pneumonia appeared. The earliest exudate in the alveoli consisted of a few large mononuclear cells and quantities of coagulated serum. Polymorphonuclear leukocytes, more large mononuclear phagocytic cells, and red blood cells are shortly added to this and appear imbedded in a meshwork of fibrin. The red color of the lung would appear from these studies to be largely due to the engorged capillaries than to free blood. At this time the interstitial lesions were much less prominent than before red hepatization had occurred. The margins of the advancing consolidation continued to show a primary interstitial character of the lesion, and the lumina of terminal bronchioles at the margin were clear of exudate while those lying within the consolidated area contained an exudate like that found in the alveoli. The transition from red to gray hepatization began in the oldest areas of consolidation near the hilus. The picture here was the familiar one so often encountered in lobar pneumonia. At this stage the interstitial reaction had become much less conspicuous. And, as is true in lobar pneumonia in the human, necrosis of the alveoli structure and air passages and thrombosis of vessels were not found. The animals dying late in the disease, or killed shortly after clinical recovery, showed the alveolar exudate to be

undergoing rapid disintegration. It was in every way similar to the picture of resolving pneumonia in the human. Finally it was interesting to note that along with resolution a variable degree of organization was always found. This was present in the perivascular tissues though variable in amount, and likewise to some degree about the bronchi. There were some instances of organization of the exudate. The newly formed fibrous tissue was found covered by a thin layer of epithelium apparently derived from the alveolar lining. The pathogenesis of lobar pneumonia as described by these authors is best followed by briefly reviewing their findings as to the presence of pneumococci in the tissues. While pneumococci were never found in the air passages save after the development of red hepatization in the surrounding tissues, they were demonstrated beneath the bronchial epithelium and in the peribronchial and perivascular stroma three hours after an intratracheal injection. Further, in 2 monkeys, with abortive attacks of pneumonia (recovery on third and fourth days respectively), autopsies immediately after recovery showed a purely interstitial pneumonia without hepatization. The spread of pneumococci from the initial site of invasion of the interstitial tissues near the hilus was entirely by interstitial tissues and lymphatics as far as the alveolar walls where they may be seen prior to an exudation into alveoli. And pneumococci were found free in alveoli as soon as the serous exudate appeared there, and before there was any cellular exudate. They therefore preceded any development of hepatization. During the progress of the above work a considerable amount of spontaneous pneumonia occurred among the stock monkeys. (iii, *Jour. Exper. Med.*, 1920, xxxi, 499). Where possible these were studied clinically and autopsies were performed in all fatal cases, the bacteriological findings in heart's blood, lung, and bronchi being worked out at the same time. It is interesting and definitely in support of the experimental method, to note that spontaneous lobar pneumonia in monkeys is identical with that produced by intratracheal injection of pneumococci, and with lobar pneumonia in man. The outbreak further was shown to have epidemiological interest in that it illustrated how the spread of infection by contact may be accomplished when conditions are favorable. In conjunction with the production of experimental pneumonia in monkeys, Blake and Cecil (iv, *Jour. Exper. Med.*, 1920, xxxi, 519) studied the results of prophylactic vaccination against pneumococcus pneumonia in monkeys. Both saline vaccine and lipovaccine made from a strain of pneumococcus type i were employed. The former gave better results; at least it appeared to have a favorable action in preventing pneumococcus septicemia. No protection was afforded by either type of vaccine against subsequent attacks of pneumococcus pneumonia, and no cross protection against other types of pneumococcus could be demonstrated. The development of active immunity against experimental pneumococcus pneumonia in monkeys following vaccination with living cultures of pneumococci was also tried (v, *Jour. Exper. Med.*, 1920, xxxi, 657). This method has been shown by various workers to have some success against other pathogenic bacteria, and the facility with which monkeys could be exposed to experimental pneumococcus pneumonia made them an excellent subject for the study of the method in pneumococcus infection. Both virulent and avirulent strains were employed, the latter in large doses. It was

found that either strain used as a living vaccine in appropriate doses protected monkeys against experimental pneumonia due to the same type of pneumococcus. And a certain amount of cross immunity is conferred by vaccination with cultures of pneumococcus type i. This method is not without its dangers, as a severe and even fatal pneumococcus septicemia frequently followed the use of a vaccine made from virulent pneumococci. It is noteworthy, too, that the active immunity against pneumococcus produced by this method of vaccination, appeared to be independent of the presence or absence of agglutinins or protective bodies in the serum. The animals which recovered from experimental pneumococcus pneumonia were tested for the degree of active immunity conferred by the disease itself (vi, *Jour. Exper. Med.*, 1920, xxxi, 685), by a second intratracheal inoculation. It was found that a high degree of immunity against the homologous type had been obtained, but that little protection was afforded against other types. As regards type iv pneumococcus pneumonia there was no appreciable immunity against the same or homologous strains of pneumococcus type iv. A study was made of the efficacy of type i antipneumococcus serum in the treatment of monkeys with experimental type i pneumococcus pneumonia (vii, *Jour. Exper. Med.*, 1920, xxxii, 1). It was found that intravenous injection of this serum promptly and permanently cleared the blood of pneumococci, shortened the course of the disease, and greatly modified its severity. Better results were obtained when the serum was administered early and at frequent intervals. When the serum treatment was started later in the course of the disease it was found necessary to continue the injections of the serum over a longer period. It is worth while to note that the control animals in these experiments all died and, further, that normal horse serum exerted no beneficial effect. Since particular interest attaches to the pathology of hemolytic streptococcus pneumonia following recent epidemics of this disease, Blake and Cecil considered that it would be of value to attempt the experimental production of this type of pneumonia (viii, *Jour. Exper. Med.*, 1920, xxxii, 401). The same method of experimental infection was carried out, but as the hemolytic streptococcus is much less virulent for monkeys, it was necessary to use a larger dose of organisms, the organisms from 0.1 c.c. to 10 c.c. of an eighteen-hour plain broth culture being suspended in 1 c.c. of fluid for intratracheal injection. Pneumonia was consistently produced in normal monkeys by this method and it had characters comparable with those of hemolytic streptococci pneumonia in man in respect to the clinical history, complications and pathology; that is, an interstitial pneumonia and a confluent lobular pneumonia were both encountered and were frequently found in the same animals. The type of pneumonia appeared to be dependent upon the amount of streptococcus culture injected, since with the injection of a small amount of culture the interstitial type was produced while the confluent lobular type followed the injection of a large amount of culture. The former was characterized pathologically by a cellular reaction, chiefly of mononuclear type in the framework of the lung. The blood remained sterile. The latter, following the injection of the organisms from 5 c.c. or more of culture, showed a confluent lobular distribution of the pneumonic exudate with areas of lax consolidation. There was a mononuclear cell reaction, and a proliferation of fibroblasts and alveolar

epithelium. With very large doses the tissue showed less evidence of resistance. The pneumonia had a lobular distribution, but the areas of exudate were widespread and confluent and the lung tissue involved showed all grades of reaction from edema to consolidation. The striking point of difference between this and pneumococcus pneumonia is seen in the power of the streptococcus to produce marked local injury to the tissue resulting in extensive damage to the walls of the bronchial tree and in widespread areas of alveolar necrosis. Further, as an end-result, there was a tendency for extensive organization to take place. In these cases a terminal invasion of the blood stream by streptococci occurred. The mode of invasion of the lung was the same as with pneumococcus pneumonia, though the type of reaction thereafter had the important differences noted. These writers differ with McCallum in regard to the pathogenesis of streptococcus pneumonia, indicating that the infection invades at or close to the hilum as in pneumococcus pneumonia and is not a primary terminal bronchiolitis. Finally, they found that irritation of the bronchial tree by chlorine gas or lowering of the animal's natural resistance by an intraperitoneal injection of Bacillus influenzæ prior to the intratracheal injection greatly facilitated the invasion of the lungs by Streptococcus hemolyticus. In continuation of the experimental studies of acute respiratory diseases, the effect of inoculation of Bacillus influenzæ into the upper respiratory tract as well as by the intratracheal route next claimed the attention of these investigators. The two final papers of the series (ix, *Jour. Exper. Med.*, 1920, xxxii, 691, and x, *Jour. Exper. Med.*, 1920, xxxii, 719) are devoted to the report of this work. A strain of influenza bacillus isolated from the pleural exudate in a case of pneumonia with empyema following influenza was utilized in this work. The virulence of the culture was raised by passage through a series of mice and monkeys. In those animals in which the nasal mucosa was swabbed with a culture of Bacillus influenzæ an acute respiratory disease followed in most instances. This was of short duration, lasting from three to five days, and was characterized by sudden onset with prostration, the development of sneezing and a cough due to rhinitis and a tracheobronchitis. The febrile reaction was variable and the white blood cell count showed a leukopenia, or sometimes no change. An acute purulent sinusitis was a common complication. In certain of these animals hemorrhagic edema of the lungs, bronchiolitis, and bronchopneumonia also developed. In those receiving the injection of virulent Bacillus influenzæ directly into the trachea, an experimental bronchiolitis and hemorrhagic bronchopneumonia developed in three out of five animals injected. In either type of experimental Bacillus influenzæ infection the influenza bacillus could be recovered by culture in the acute stage either pure or associated with other bacteria. In general, both clinically and pathologically, the processes closely resembled on the one hand simple influenza, and on the other uncomplicated Bacillus influenzæ pneumonia in man. It is noteworthy that experimental Bacillus influenzæ infection can be initiated by a simple swabbing of the nasal mucosa. This indicates a property of invasiveness not possessed by the pneumococcus or by the Streptococcus hemolyticus, as this method of experimental infection with these organisms was shown in the earlier papers to be unsuccessful. Another characteristic difference between Bacillus

influenzæ and pneumococci or Streptococcus hemolytic infections is seen in the mode of extension in the respiratory system. Inoculated into the upper air passages it extended throughout the mucosal surfaces of these regions, with the result that sinus infections were frequent; here we have another point of resemblance to the disease in man. Further, it was even shown in a number of instances that the simple instilling of cultures of Bacillus influenzæ into the upper air passages also resulted in its extension downward to the finer ramifications, with the development of a terminal bronchiolitis followed by acute inflammatory edema and bronchopneumonia. This mode of spread by continuity along the epithelium of the air passages is in direct contrast to the mode of extension in the case of pneumococcus or Streptococcus hemolyticus, in which the organisms early invade the lymphatics and subsequently extend in these channels. These latter experiments are advanced as evidence in favor of the etiologic relation of Bacillus influenzæ to influenza. As the authors state, it seems reasonable to infer from this work that the influenza bacillus is the cause of influenza. They add, however, that a definite conclusion is not permissible, since it is impossible to determine whether the experimental disease is identical with it or only similar to it.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Investigations of the Germicidal Value of Some of the Chlorin Disinfectants.—TILLEY (*Jour. Agri. Research*, October 15, 1920, No. 2, vol. xx) found that in the ordinary routine work of general disinfection, such as disinfection of cattle cars and pens, there is always a large amount of organic matter present. It is evident, therefore, that because of the enormous diminution in germicidal value on addition of organic matter, as well as because of the injurious effects on metals and fabrics, the chlorin disinfectants, as a class, do not seem to be suited for use under the usual conditions and by the usual methods of general disinfection. That is not to say, however, that when properly used they are not efficient and valuable in the treatment of infected wounds; in fact, the evidence available goes to show that they are of great value when so used; and, of course, chlorin and hypochlorites are being very widely and successfully used for the disinfection of drinking water. Compared on a basis of weight of chloramin-T as against the weight of chlorin, as sodium hypochlorite

(Dakin's solution), or hypochlorous acid (eusol), or as chlorin in aqueous solution, chloramin-T is less efficient than the others. But if the comparison is made on the basis of available chlorin contained it is much more efficient against Staphylococcus aureus, much less efficient against Bacillus pyocyaneus and approximately equal in efficiency against Bacillus typhosus. The experiments upon Bacillus tuberculosis indicate that the chlorin disinfectants are worth very little so far as that organism is concerned. This is not surprising in view of the use of antiformin (NaOCl + NaOH) in isolating tubercle bacilli. In the present work, considered as a whole, there is seen throughout more or less "selective action" on the part of the various disinfectants. The most clearly defined example of this is seen in the extremely high value of chloramin-T against Staphylococcus aureus as compared with its extremely low value against Bacillus pyocyaneus. The results of the experiments upon anthrax spores show that the germicidal action of chlorin compounds is not always so speedy as is commonly supposed, but may extend over several days. The addition of ammonia to solutions of chlorin or hypochlorites very greatly increases germicidal activity and tends to prevent depreciation in value on the addition of organic matter.

Streptococci Occurring in Sour Milk.—JONES (*Jour. Exp. Med.*, January 1, 1921, No. 1, xxxiii, 13) states that a well-defined group of rod-like and coccoid organisms arranged in chains and pairs has been encountered in sour milk. The group comprises at least three species; the largest number ferment dextrose, lactose, maltose, mannitol and salicin, and fail to ferment saccharose, raffinose and inulin. A smaller number ferment saccharose in addition to dextrose, lactose, maltose, mannitol and salicin. A few fail to attack mannitol. All three types grow luxuriantly at room temperature, coagulate milk, reduce litmus, and produce large amounts of acid in fermented bouillon containing dextrose. Specific morphologic and cultural differences exist between the lactic acid streptococci and those associated with mastitis and those occurring in the udder. The lactic acid organisms outgrow the udder streptococci in the milk-souring process. When both types are implanted in sterile milk the udder type soon disappears.

Fate of Microörganisms Introduced into Isolated Loops of the Intestine.—EISKAMP and PARK (*Jour. Infect. Dis.*, January, 1921, No. 1, xxviii, 67) state that many specific microörganisms injected into isolated loops of the intestine of dogs are destroyed in periods ranging from two to seven hours. This destruction is not due to the antagonistic action of the normal intestinal flora. There is evidently a distinct antibacterial mechanism in the intestine, the nature of which is at present unknown.

Commission on Milk Standards.—The report (*Public Health Reports*, December 10, 1920, No. 50, xxxv, 2955) approves of pasteurization of milk as follows: "(*a*) That pasteurization of milk should be between the limits of 140° F. and 155° F. At 140° F. the minimum exposure should be twenty minutes. For every degree above 140° F. the time may be reduced by one minute. In no case should the

exposure be for less than five minutes. (*b*) In order to allow a margin of safety under commercial conditions the commission recommends that the minimum temperature during the period of holding should be made 145° F. and the holding time thirty minutes." Under the head of "Scurvy" the reduction of vitamines by pasteurization is recognized and the use of an antiscorbutic is recommended with the pasteurized milk. In the consideration of dried milk a liberal policy is recommended, as indicated by the following: "WHEREAS, The commission is fully convinced that an increased consumption of milk in its various forms would be highly advantageous to the public health; and WHEREAS, The production and sale of dried and remade milk tend to increase, stabilize and conserve the milk supply; and WHEREAS, All evidence now available favors the view that properly prepared dried milk may be regarded as of nutritional value equal to milk of light grade and that the vitamine content of dried milk and pasteurized milk is substantially the same: THEREFORE BE IT RESOLVED, that the Commission urge upon the health and food control officials a liberal attitude such as shall encourage and not hamper the dried milk industry."

Accuracy of the Schick Reaction.—ZINGHER (*Jour. Am. Med. Assn.*, November 13, 1920, No. 20, lxxv, 1333) states that the accuracy of the Schick test depends on the strength of the toxin, the technic of the test and the interpretation of the reaction. Errors in any of these may make the results of the test unreliable. It is possible to guard against a poor technic and a wrong interpretation of the reaction, but it is essential to be able to depend on the accuracy of the outfits for the Schick test obtainable on the market. The outfits furnished by four commercial laboratories were tested. Of five outfits of one laboratory, two contained too small an amount of toxin to give a positive reaction in Schick-positive children. Of three outfits of the second laboratory one was somewhat weaker and two very much weaker than the standard outfit, so that negative reactions were obtained in Schick-positive individuals. The outfits of the third laboratory compared fairly well with the control in the clinical test when twice the amount of toxin dilution prescribed in the directions on the outfits was injected. The animal test showed only about 85 to 90 per cent. of a minimal lethal dose in an outfit instead of one minimal lethal dose. The outfits of the fourth laboratory gave reactions similar to those noted with the control test. The outfits furnished by the Research Laboratory of the Department of Health of New York City gave practically uniform results clinically and the animal test showed full potency of the toxin. It is practicable to manufacture outfits for the Schick test on a large scale without sacrificing accuracy.

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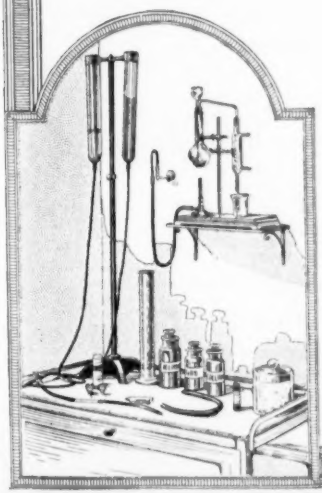

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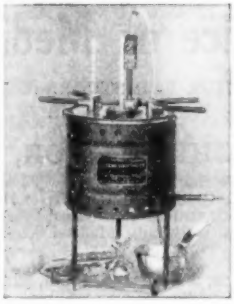

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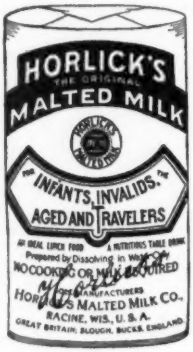

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THE growing opinion that **public health is to a large extent purchasable** has stimulated health authorities to develop their opportunities and to assume greater responsibilities. The best medical colleges no longer confine their teaching to the diagnosis and treatment of disease, but give thorough courses in hygiene, and its practical application in preventive medicine. The technological schools are providing similar courses.

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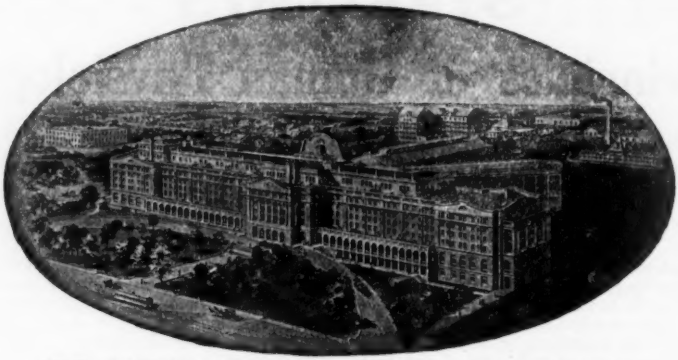

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